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FOREWORD

IT IS fitting that Carl J. Wiggers should be the first physiologist to be honored by the dedication to him of a special number of *Circulation*. In the half century since he began his work, he has properly become the dean of cardiovascular physiologists. Moreover, the school created by him has made a historic impact on the entire field. While Dr. Wiggers himself has never been able fully to pursue the active study of clinical physiology in the patient, his work in fundamental physiology of the circulation is now a basic background for much of current clinical investigation. This must be a matter of great pride and satisfaction to him. Like many another pioneer the significance of Wiggers' work, and that of his students, was fully appreciated only after a long lag. This, however, has never deterred him from continuing along the lines of endeavor he has chosen for himself.

Dr. Wiggers' career may be divided into three periods, the Ann Arbor, the New York and the Cleveland periods. Having been born in Davenport, Iowa, it was natural for him to enter the progressive midwestern medical school of the University of Michigan. Here he came in contact with one of his revered teachers, Warren P. Lombard. Here, until 1911, he taught physiology and did his early research. In 1906 he became an instructor and in the same year obtained his M.D. degree. In his last year at Ann Arbor he was the acting director of the department. This gave him an initial opportunity to emphasize the value of the application of physiology to clinical medicine—a fundamental concept he still continues to stress. He has said, "Every disease is an experiment that nature performs, and its signs and symptoms are the manifestations of abnormal functions." It was in this period that he presented his first communication before the American Physiological Society (Ann Arbor, 1905).

In 1911 he moved to New York as an instructor in physiology at Cornell University Medical School under Graham Lusk. During this period he was given leave of absence to study under Otto Frank at the Institute of Physiology, University of Munich in Germany. On his return he quickly rose to the rank of assistant professor (1913) and later, for a time, acted as head of the department when Doctors Lusk and Murlin left for war duties during the first World War. Afterwards, he himself was assigned to Army General Hospital No. 9 and there became familiar with clinical electrocardiography and disturbances of heart action.

This New York period served Dr. Wiggers in good stead subsequently. Dr. Lusk's personality left an indelible impression and broadened his perspective in physiology. But it was particularly his contact with Professor Frank that gave him direction in his life's work. From Frank he acquired a deep appreciation of the merits of accurate recording equipment and of its employment to solve the mysteries of biohydraulics. On returning from Europe he wrote, in 1915, his first monograph, *Modern Aspects of Circulation in Health and Disease*, which he revised and expanded in 1923. The pattern of his work was now established.

In 1918 he accepted the call to assume the chair of physiology at Western Reserve University and had the opportunity to set up an ideal modern department in the new medical school when it was built a few years later. For over three decades he has remained actively at work in the department which he built. While the Ann Arbor period may be said to represent

Carl J. Wiggers' adolescence and the New York period with its trip to Europe his maturation, it is in the Cleveland period that he has shown his full maturity.

Dr. Wiggers has always been a prolific writer. During his years in Cleveland several other of his monographs and the classical textbook on *Physiology in Health and Disease* (1934) have been written. He and his associates have published, up to now, over 350 research communications. A goodly number of them have been his own. Even when his name has not appeared as a co-author or in a footnote acknowledgement, his influence upon the thinking, the experimentation and the writing of these articles is quite apparent to the informed reader. He has always felt that when a young man in research has attained a certain stature, it is incumbent upon his chief not to "sign in" or even to detract from the young man's promise by having the chief's name appear in a footnote. He has always felt that each research project is the work primarily of one, two, or at most three minds and not of a large group.

Dr. Wiggers has always taken a fatherly interest in every member of his staff, whether he was high or low in rank. This has included interest in their scientific activity, their academic career and even their domestic affairs.

He is devoted to his life work and considers administrative and committee work a necessary evil detracting from his primary objectives, research, teaching and training of young investigators and teachers. He has always worked hard, putting in a full day at the school. Even after leaving the laboratory, he is to be found on many occasions working in his library until the small hours of the morning.

Since he works hard himself and is always prompt, Dr. Wiggers hates tardiness, sloppiness and "spoon-feeding" in others. An example of his industry and attitude is shown by the fact that before he went to South America on tour he learned Spanish within a few months so that he himself could lecture in that language rather than through an interpreter. He has always been frank and maintained his intellectual honesty; he has never compromised his views either privately or in public regardless of the persons involved. He has retained the devotion of his associates, the respect of his colleagues and the warm friendship of an extraordinary number of people.

In the course of the years Dr. Wiggers has received many honors and become a member, regular or honorary, of many scientific societies here and abroad. Of many of these he has been an officer or director. But perhaps the honor which gave him greatest pleasure was his elevation to the presidency of the American Physiological Society. His identification with the cardiovascular field is not only through teaching and research, but by active participation in the functions of the American Heart Association and its several councils, as well as the Interamerican and International Cardiological Societies. Other honors have come in great numbers to Dr. Wiggers, including the honorary degree of Doctor of Science given him in 1941 by the University of Michigan, his Alma Mater, and his recent election to the National Academy of Science.

Of even greater satisfaction must be the knowledge that he has had a vast influence on medical thinking in the cardiovascular field through his research, his teaching and the body of scholars that he has brought up. He is a great teacher and a great creator of disciples. Hence it is no chance event that his numerous associates have attained important positions in this country and abroad and they, following in the footsteps of their master, have helped him to change the perspectives and to advance greatly the frontiers of knowledge in this field of medicine, physiology and research. Of particular gratification to him must be the fact that one of his two children, Dr. Harold C. Wiggers, one of his most active students, is following so promisingly in his footsteps.

The unique trainee school for young investigators created a few years ago by Dr. Wiggers, with the joint support of the American Heart Association and the National Heart Institute, gives him great joy. It has been contributory in continuing the flood of Wiggers-trained students to the cardiovascular field.

I know that all his students agree that of many rich experiences none has been so satisfying as that of working with Dr. Wiggers.

LOUIS N. KATZ

Determinants of Cardiac Performance

By CARL J. WIGGERS, M.D., SC.D.

Sequential experimental studies are reviewed which, when properly integrated, confirm the concept that the responses of the ventricles, however measured, are determined by the initial length of fibers, provided that the functional state of the myocardium is not altered. Some of the established factors are discussed which may obscure the evidence that this basic law is of importance under normal and pathologic conditions.

DURING the past 50 years progress in the study of heart disease has been achieved over different pathways.[1] Among these is the clinical application of instrumentations and technics originally designed in, and limited to, physiologic laboratories. Since my entry into medical school in 1901 I have witnessed the successive employment of sphygmographs, phlebographs, apex beat recorders, sphygmomanometers, plethysmographs, roentgenographs, electrocardiographs, and phonocardiographs. Some of these have not survived the dictates of experimental fashions and are known to the present generation only as museum pieces or text figures,[2] if at all. They were retired from the armamentarium of clinicians because the information gained did not appear commensurate with the time and effort required for their proper use. With the development of high fidelity pressure recorders in laboratories and the demonstrated safety of arterial punctures[3] and cardiac catheterization in hospitals[4] we have entered an era in which circulatory derangements are being intensively studied through the interpretation of cardiac outputs and of pressure pulses recorded directly from the cardiac chambers and large vessels. The interpretation of circulatory dynamics by such procedures requires not only a comparison of data from human subjects in health and disease, but also the utilization of information derived from more controllable experiments on animals. We can obviously not hope to comprehend the processes through which we die unless we understand the mechanisms which keep organisms alive.

The purposes of this review are (1) to restate briefly some important experimental results on cardiac performance, (2) to re-examine concisely the deductions, theories and concepts of cardiac behavior to which they have given rise, and (3) to attempt a resynthesis of evidence into a modern physiologic concept of myocardial regulation. Such a process of "modernization" involves a divorcement of factual data from theories and the integration of successive discoveries with classical ones of the past. When this is done it frequently happens, as in this instance, that very old laws of cardiac behavior have merely been given more extended applications, rather than that essentially new ones have been discovered.

THREE CLASSIC DISCOVERIES

1. In 1869 a young American, Dr. H. P. Bowditch, undertook the study of physiology in Ludwig's laboratory in Leipzig. His investigation on the apex of the frog's ventricle published in 1871[5] has become a classic in physiology. He showed that if the condition of the heart muscle remains unaltered, the contractions remain equal regardless of the strength of stimuli applied. As Ranvier[6] expressed it, the heart's motto is "all or none." The paradox that the ventricles can obviously alter the vigor of their contractions, under normal as well as pathologic conditions, was explained by another observation in the same investigation, namely, that excitation of the resting frog's ventricle by successive shocks *of the same intensity at short intervals* results in a progressive increase in amplitude of contractions. The phenomena called "treppe" or "staircase" is obviously occasioned by the fact that

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each stimulus exerts a beneficial aftereffect on the responsiveness of cardiac muscle.

Summarizing, the law of all or none implies that cardiac muscle either does not contract at all or responds to the fullest extent, but the magnitude of the all or none response is determined by the inherent "condition" of the muscle.

2. In 1884, Howell and Donaldson[7] presented unequivocal evidence that the heart itself has intrinsic mechanisms by which its output is nicely adjusted to the venous input. Using the Newell Martin heart-lung preparation, it was found that augmentation of venous inflow to a heart weighing 76 Gm. caused the cardiac output to increase from 480 to 1964 cc. per minute, the stroke volume from 5.2 to 21.6 cc., and the right atrial pressure from 10 to 60 cm. of blood. The compensation for increasing volumes of venous return was not quite perfect, however; increases in output of the left ventricle lagged progressively behind the available supply of blood in the venous reservoirs. Upon reducing venous inflow so that atrial pressure fell to the original level of 10 cm. of blood, cardiac output dropped to 400 cc. and the stroke volume to 2.38 cc., which indicated that the performance had deteriorated slightly after a short period of strain.

3. In 1895, O. Frank[8] published his investigations on "the dynamics of heart muscle." His object was "to correlate as far as possible the mechanical reactions of cardiac muscle with the well known responses of skeletal muscle previously established by A. Fick, J. von Kries, and Blix." It should be recalled that these investigators had established a relationship between the force of contraction and the degree of stretch and tension under which skeletal muscles were placed previous to stimulation, that is, the so-called initial length and tension. Frank recorded isometric and isotonic contractions of the frog's atria and ventricle during various degrees of diastolic filling and pressure. He found that, within limits, stepwise increases in diastolic volume and pressure just before contraction—hereafter called the *presystolic volume and pressure*—determine the magnitude of the all or none response. These studies emphasized that the cardiac response to artificial or natural excitation is determined wholly by hemodynamic events which precede excitation.

Years of experimentation have not only confirmed the basic laws of cardiac behavior founded upon these observations, but they have also elucidated the many variables which tend to obscure their operation in the control of the mammalian heart under normal and pathologic conditions.

The Law of Uniformity of Behavior

In 1906, Y. Henderson[9] succeeded in improving previously used plethysmographic technics sufficiently to establish patterns of ventricular filling and emptying under different circulatory conditions. A study of cardiometric records led Henderson and his associates[9] to the conclusions (1) that the ventricles have a fixed pattern of relaxation which determines their diastolic capacity as long as the venous supply is at normal levels, and (2) that further increase in venous supply cannot augment ventricular filling and systolic discharge. Such a concept set an extremely low limit to the cardiac response to increasing initial tension and length. According to this view also the only way in which greater volumes of venous blood could be pumped to the aorta would be through an increase in heart rate. According to his "law of uniformity of behavior," cardiac output increases progressively up to rates of 180 per minute, thereafter becoming stationary and, during extreme tachycardia, diminishing rapidly.

A reappraisal of Henderson's work indicates that his analysis of ventricular volume curves gives a valuable geometric plan for evaluating the effect of cycle length on systolic discharge and cardiac output; but his conclusion that increased venous return cannot augment ventricular filling does not seem to have been supported by valid experimental evidence. Henderson was unquestionably correct in his deduction that ventricular filling occurs largely in early diastole as a result of A-V pressure differences, but he underestimated the additional quantity of blood that the atria inject into the ventricles, partly because the slower

beats in his experiments were obtained during vagus stimulation and therefore associated with depression of atrial contraction.

The Applicability of Laws of Initial Tension and Length to Mammalian Hearts

In 1914 the writer[10] reported experiments which demonstrated that every increase or decrease in volume of blood returning to the right atrium simultaneously alters the initial tension, height, and contour of the right intraventricular pressure curve. These experiments were the first to demonstrate that the reactions established for the frog's ventricle are also applicable to the naturally beating right ventricle of dogs. In brief, the conclusion was reached that the gradient of the isometric pressure rise and the peak systolic pressure are determined by changes in the initial tension, as long as marked changes in inherent contractility are not simultaneously produced by experimental procedures.

Concurrently and quite independently, other investigators, notably Starling and his associates[11] and Straub,[12] investigated the effect of changes in initial tension and length on the response of isolated hearts. Since the work of Starling and his group has aroused the greatest attention in relation to clinical studies, a reappraisal of their investigations and conclusions should be of timely interest. These investigators utilized their well known heart-lung preparation[13] which was designed to control heart rate, mean arterial pressure and venous inflow, and to vary any one of these factors at a time. This was of signal importance despite the facts that the individual factors cannot be controlled as independently as the British investigators believed and that the dynamic conditions under which the heart operates deviate somewhat from those which exist in the body.[14–17] The important results and conclusions pertinent to our discussion can be summarized as follows:

1. When arterial resistance and venous inflow were kept constant—within limits of the preparation—variations in heart rate from 60 to 160 per minute caused no significant changes in cardiac output per minute (Markwalder and Starling[11]), a conclusion diametrically opposed to that of Henderson and his associates.[9] The inference was drawn—and later it was supported in a measure by registration of volume curves—that ventricular filling is not dominated by a fixed pattern of relaxation and elastic resistance to filling pressures (Patterson, Piper and Starling[11]).

2. At constant heart rate and mean arterial pressure, progressive augmentation of venous inflow caused progressive increases in diastolic size (stretch), systolic discharge, and cardiac output per minute up to a critical atrial pressure (compensation). Beyond this, systolic discharge and cardiac output decreased (decompensation). These results were interpreted as follows: A compensatory increase in stroke volumes takes place *as long as the ventricles can undergo additional distention*. When no further distention is possible, owing to limitations imposed by the elastic ventricular stretch or the restraining action of the pericardium,[18] the rapidly increasing presystolic tension exerted on individual fibers hinders the development of contractile force, and systolic discharge diminishes (Patterson, Piper and Starling[11]).

3. During the compensatory state, that is, while cardiac output increased with augmenting venous supply—pressures rose *pari passu* in both atria, slowly at first and thereafter at a progressively increasing rate. During the stage of decompensation (when cardiac output of the left ventricle began to decline) pressure rose rapidly in the right atrium but fell in the left (right heart failure) (Patterson and associates[11]).

4. The fatigued or depressed heart could have an output equal to that of a fresh heart but required a higher atrial pressure and greater presystolic ventricular distention. The corollary follows that, at controlled heart rates, the competence of the myocardium may be tested by comparing the systolic discharge at equivalent venous pressures or by determining the venous pressure required to produce equivalent stroke volumes. This procedure has been used by Krayer[16] in the heart-lung preparation and by the author[19] in the intact animal.

5. In some experiments in which simultaneous volume and pressure curves from the ventricles were recorded, it appeared that considerable increase in presystolic ventricular size took place, while the presystolic or initial tension in the left ventricle remained unchanged or actually fell (Patterson, Piper and Starling[11]). However, at the time these investigators worked it was not realized that slight shifts in the entire pressure curve cannot be excluded unless a base line for optical pressure curves is simultaneously recorded. From their observations the inference seemed warranted that the presystolic size (stretch) of the ventricles is not determined solely by actual filling pressures (mean atrial pressures), but is affected also by inherent variations in their rate of relaxation and elastic or tonic resistance to stretching. On the whole, they believed that the mammalian ventricle, unlike that of the frog studied by Frank, rarely reaches a state of "static relaxation" before the succeeding beat supervenes.

From these observations, Starling's oft quoted "law of the heart" was derived.[20] There is a general impression that the graphic representation of the law, often reproduced, was based on data from these experiments. The careful reader will discover the frank statement that the published curves are reproductions of graphs previously published by Blix and by O. Frank (Patterson, Piper and Starling[11]).

"So far our analysis of the mechanical condition of the heart's contraction does not differ essentially from Frank's classical exposition of the mechanical events affecting contraction of the frog's heart. In this work, however, Frank was dealing with contractile tissue which had long periods of diastole, so that it had reached a static condition before the beginning of systole, and he found that the energy set free in the excited condition (as measured by the tension set up) was proportional to the initial, i.e., diastolic, tension on the muscle. But in this case it is not easy to decide whether the determining factor is really the initial tension or the initial length of the muscle fibres. . . .

"In the mammalian heart we are dealing with an organ which is contracting rapidly and rhythmically, such contraction being a necessary condition for the preservation of its functional activity. The condition of the heart therefore as to both tension and length of its muscle fibres is altering continuously during diastole from one beat to the next.

"In Frank's experiments on the frog's heart, the initial length was proportional to the initial tension, so that the augmentation of energy set free on contraction might have been due either to the increased tension or to the increased length. In our experiments we have found that it is length rather than tension which determines the energy of contraction.

"We thus find no constant connection between the diastolic tension and the succeeding contraction, though as a rule these two quantities will be altered together. But we do find a direct proportion between the diastolic volume of the heart (i.e., the length of its muscle fibres) and the energy set free in the following systole.

"The law of the heart is therefore the same as that of skeletal muscle, namely, that the mechanical energy set free on passage from the resting to the contracted state depends on the area of 'chemically active surfaces,' i.e., on the length of the muscle fibres. *This simple formula serves to explain the whole behaviour of the isolated mammalian heart,—its movement, powers of adaptation to varying demands made upon it, its behaviour to fatigue and the influence of its nerves or chemical agencies such as acid ions or adrenalin.*" (*Author's italics.*)

The basic idea underlying Starling's law of the heart, namely, that myocardial response is determined basically by the degree to which fibers are stretched, has been supported, with one exception,[21] by all subsequent investigators.[22–31] However, attention may be directed to the fact that all investigators have assumed the existence of a linear relation between presystolic ventricular capacity and length of fibers, and between presystolic intracardiac pressure and initial tension on muscle fibers. The validity of this assumption for the mammalian ventricles composed of complicated superimposed muscle bands arranged to pull in different directions has never been adequately established.

In 1922, Katz and I[32] restudied the mechanism of adaptation to increasing venous return by means of cardiometric technic in a controlled circulation preparation. The preparation, as progressively improved in subsequent researches, is diagrammatized in figure 1. The heart of a lightly anesthetized dog is exposed under artificial respiration just enough for the animal to retain natural diaphragmatic movements. This offers a simple indication that blood gases remain essentially normal. The cardiac nerves are severed. The heart rate is controllable within

wide ranges; it is reduced to 40 or 50 per minute by clamping the sinus node and then driving the heart by electric shocks applied to the right atrium. Venous return can be decreased through graded compression of the inferior vena cava or increased by an infusion of warm saline into a jugular vein. The reduction in blood viscosity which accompanies such infusion is advantageous dynamically, for it has proved just about sufficient to maintain a constant diastolic pressure despite increasing stroke volumes. Arterial resistance can be controlled by tightening or loosening an adjustable clamp placed around the lowest portion of the thoracic aorta.

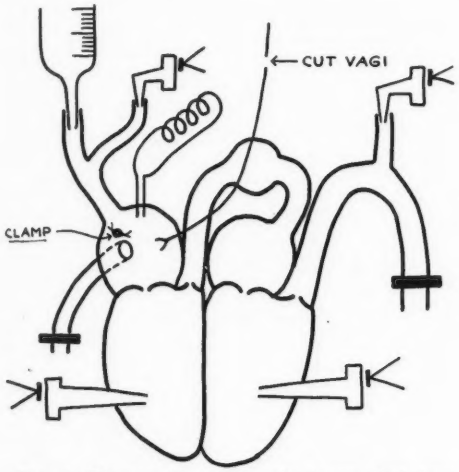

FIG. 1. Diagram illustrating the "controlled circulation preparation" for studying separate determinants of ventricular response. Discussion in text.

Volume curves of the ventricle are recorded optically together with arterial pressure pulses as described elsewhere.[2, 32] Typical curves are shown in figure 2. The volume tracings descend with diminution of ventricular volume during systole and rise during diastolic filling. Changes in slope (1–9) indicate changes in the rate of ventricular emptying and filling. During the phase of isometric contraction (2–3), the curves either rise or fall slightly. These variations are unavoidable artefacts created by slight shift of the cardiac base with respect to the rubber diaphragm. During systolic ejection (3–7) several changes in rate of emptying corresponding to inflections of the aortic pressure curve are indicated by vertical lines. The rapid ejection rate from 3–6 and the marked reduction from 6–7 are particularly noteworthy. Systole ceases at 7 and the interval 7–8 demarcates the isometric relaxation phase of the ventricles. Ventricular filling occurs rapidly at first (8–9) and then more gradually (9–1), dividing the filling into phases of rapid inflow and diastasis. This is followed by atrial systole (1–2).

The results obtained by Katz and myself[32] in the main confirmed those of Starling and his

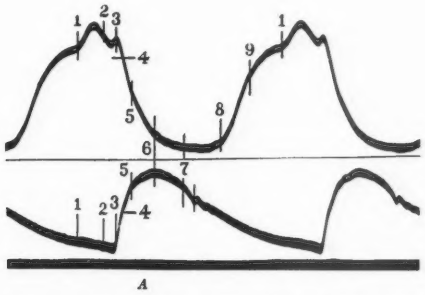

FIG. 2. Simultaneously recorded volume curve of ventricles (upper) and aortic pressure (lower) showing corresponding inflections during phases of ejection and division of systole and diastole into commonly accepted phases: (1–2) atrial systole, (2–3) isometric contraction, (3–5) period of maximal systolic ejection, (5–7) period of reduced systolic ejection, (7) end of systole, (7–8) isometric relaxation, (8–9) rapid diastolic filling, (9–1) retarded diastolic inflow (diastasis).

group, but some amplification and certain differences were found:

1. During the compensatory stage of increased venous return (compare curves A and B in fig. 3) ventricular filling proceeded more rapidly throughout diastole, that is, during the successive periods of rapid inflow, diastasis and atrial contraction, and the larger systolic discharge was accomplished by a greater velocity of ejection, a prolongation of the ejection period (compare A and B), and occasionally even more complete emptying. It is obvious at a glance that such curves are not superimposable as regards either their systolic or diastolic limbs. Optical pressure curves from the right ventricle (lower series, fig. 3) demonstrated that the presystolic intraventricular pressure (initial

tension) increased steadily, the gradient of pressure before ejection (isometric phase) was steeper, and the curves reached higher peaks. The larger volumes ejected by the right ventricle under higher pressure necessarily caused an elevation of left atrial pressure. Contrary to Starling's observations, Opdyke and his associates[33] have recently demonstrated that the increase in pressure was much larger in the left than in the right atrium, owing to a lesser distensibility of the left atrium and its tributary veins.

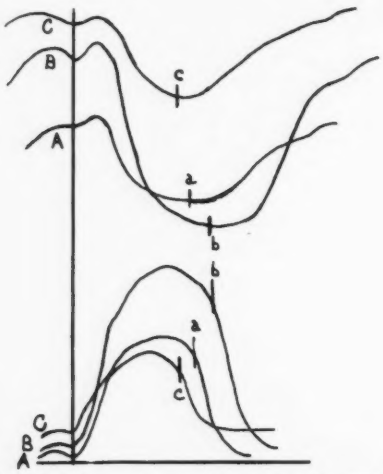

FIG. 3. Changes in configuration of ventricular volume curves (upper series) and right ventricular pressure pulses (lower series) during progressive increase in rate of venous return. All curves matched at beginning of ventricular systole; a, b, c denote ends of systole and illustrate changes in relative durations of systoles. (A) control, (B) during compensatory stage, (C) during decompensatory stage.

2. Contrary to interpretations by Starling and his associates, we found that reduction in stroke volume with excessive rates of venous inflow was not conditioned by the fact that the ventricles had reached their distention limits; decompensation developed while the process of diastolic distention was actually accelerating (fig. 3B, C). In other words, it appears that beyond a critical degree of stretch, additional extension either has a reversed effect on the release of mechanical energy or contraction is hindered by the greatly increasing diastolic tension. This also accords with O. Frank's observations on frog hearts[8] and with those of Lundin[34] on stretched moieties of ventricular muscle. Analysis of volume and right ventricular pressure curves (fig. 3C) indicated that, despite a large increase in diastolic size and in initial tension, the mechanism of discharge changed, the ventricles emptied themselves less forcibly and completely; indeed, the systolic size was sometimes smaller than the normal diastolic size. An enormous increase in residual volume was apparent (see a and c, curves A and C), indicating that a considerable effective volume of blood stagnated in the heart during progressive decompensation. The systolic pressures in the right ventricle and pulmonary artery decreased and, consonant with Starling's results, pressure in the left atrium fell.

3. With constant venous return and right atrial pressures, the cardiac output was found to be far from constant at different heart rates, as the British investigators claimed. Under carefully controlled atrial pressure the alterations in stroke volume with progressive acceleration followed the predictions of Y. Henderson rather better than the experimental results of Starling and his group. However, unless arterial and venous pressures were readjusted with every change in heart rate, the beats were not superimposable and accurate predictions as to the relation of cardiac output to heart rate could not be made.

The reasons for the variable effects of heart rate changes on stroke volume and cardiac output per minute have gradually become clearer from the study of a large number of ventricular volume curves. The integration of a large number of physical and physiologic determinants on ventricular filling are involved. An attempt is made to dissociate the chain of events with the aid of the diagram in figure 4. The heavy curve (N) represents a ventricular volume curve under normal conditions at a heart rate of 75 per minute. The record is taken in such a manner that ventricular emptying is indicated by the downstroke and filling by the upstroke. The residual volume is indicated without ordinate values. The phases of systole and diastole for this beat are numbered as in figure 2.

An acceleration of the heart approximately

to 120 per minute would, according to Y. Henderson's scheme, merely cut into the filling curve as indicated by the arc A. This, however, is an oversimplification of changes that actually take place. In the first place, despite constancy in returning blood volumes, such acceleration very quickly reduces the pressure and volume of blood in the atria in a mechanical way. Simply stated, more blood is pumped per minute than is received. As a result, the rate of the increment becomes somewhat greater as indicated in the wave Y which may restore the systolic stroke C approximately to that of stroke A. Necessarily the diastolic filling curves are not superimposable, but the net effect on stroke volume approximates Henderson's predictions. If, in addition, the increase in heart rate is induced by activation of the accelerator mechanism and release of the vagus mechanism, the force of atrial systole may be increased

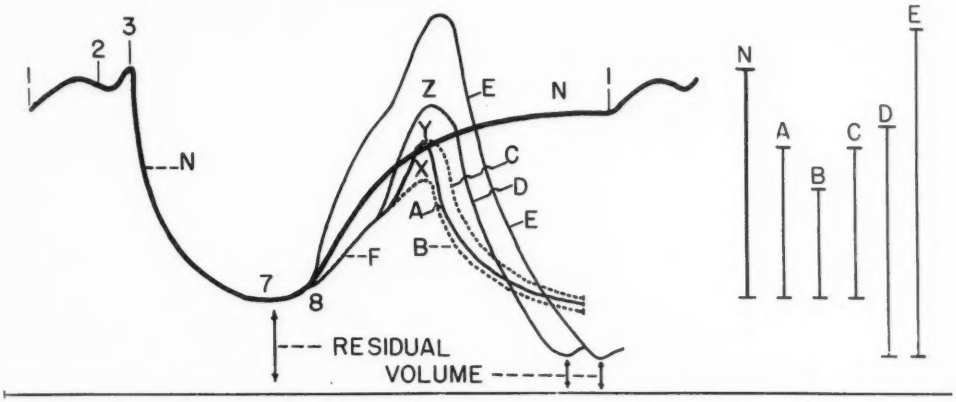

FIG. 4. Heavy curve (N) typical volume curve for heart cycle, 0.8 second (75 per minute). Numerals same as in figure 2. Assembly of superimposed ventricular volume curves illustrate variable factors that may influence stroke volume when heart rate increases to 120 per minute. (A) Abridgement of natural filling and reduction of stroke volume, according to Henderson. (B) Further reduction in systolic discharge owing to coincident reduction in atrial pressure and reduced filling rate shown at F, and diminished force of atrial systole at X. (C) Restoration of stroke volume to control of curve A by greater effectiveness of an atrial systole (Y) which supervenes immediately after or during rapid inflow. (D) Increase in stroke volume to that of a beat with long cycle (N) as a result of accelerator nerve action or adrenergic humoral effects which increase force of atrial contraction Z, and more completely empties the ventricles (reduction of residual volume). (E) Further augmentation of systolic discharge through simultaneous increase in venous return and more rapid filling as in exercise. Lines on right (N–E) indicate at a glance comparative stroke volumes for corresponding volume curves.

filling during the rapid inflow phase tends to become more gradual, as in the curve labeled F. Since the atria start their contractions at a shorter initial length the vigor of their contractions would be diminished, and it might be expected that their contribution to ventricular filling would be reduced, as indicated in the wave X. However, this diminishing effect of atrial contraction appears to be offset by the fact that atrial contractions coming at the time of incomplete ventricular filling are more effective than those that occur after a long diastasis, as in the solid line curve. As a result, significantly and the contribution to ventricular filling may be represented by wave Z. Under such hypothetic conditions the stroke volume D may almost equal that of the control beat N, for the accelerator mechanism also acts directly on the ventricles to reduce their residual volumes.

Such an approximate proportionality of cardiac output to heart rate can obviously be maintained only as long as the volume of venous return equals the cardiac output. If as a result of many conditions—hemorrhage and shock, for example—this is not accomplished,

these compensatory reactions cannot be maintained. If, on the other hand, venous return augments at the same time that the heart accelerates, as in exercise, the stroke volumes can definitely exceed the normal, as illustrated in curve E. This analysis of the many coefficients which affect ventricular filling explains why investigators have differed (a) as to the contribution of atrial systole to ventricular filling, and (b) as to the effect of heart rate changes on cardiac output per minute.

It seems apparent now that the constant cardiac outputs obtained by Starling and his associates over wide ranges of heart rates were due to a fortuitous balance between these variable factors. The British investigators failed to recognize that the available supply and pressure of blood in the right atrium is determined as much by changes in cycle length as by the pressure head in a venous reservoir. Furthermore, as Krayer[18] has pointed out, these investigators altered heart rate through changes of temperature of the inflowing blood which is certainly not without influence on the inherent contractility of the ventricles.

Intrinsic Cardiac Factors. Our analysis of the relationship between atrial volumes and pressures, duration of the inflow periods and force of atrial contractions on the one hand, and systolic discharge and cardiac output per minute on the other, accord basically with the law of initial length. The resultant effect of filling pressure, atrial activity, and the available filling time regulate the degree of ventricular distention (initial length) realized at any given cycle length, and this in turn determines the velocity, volume, and duration of the systolic discharges. However, this is only a first approximation to reactions of the heart muscle at a given initial length in the body. As Starling and his group pointed out, at equivalent initial lengths a heart in good condition responds with a larger stroke volume than a fatigued heart. Also as Katz and I[32] pointed out the pattern of ventricular emptying is not solely governed by presystolic filling, but it is also affected by reduction in coronary flow.

Hearts stimulated or depressed by drugs, chemical changes in the blood, or through nerve actions show similar variations. In a study of the dynamics of drug actions I pointed out in 1927[35] that the vigor and pattern of ventricular contraction and consequently its systolic discharge can be influenced (a) by agents which primarily affect the contractility of the myocardium as well as (b) by those which secondarily affect contractility through changes in initial tension or length such as are induced by alterations in venous return, arterial resistance, and heart rate. To the latter may be added hydrodynamic effects produced by such pathologic conditions as coronary insufficiency, valvular lesions, anomalous cardiovascular circuits, pulmonary vascular changes, and pericardial effusions. In short, the ventricles do not obey the "law of all or nothing" at any given degree of fiber stretch; their magnitude of response depends on the physiologic state of myocardial reactivity. Starling was certainly aware of the importance of the "condition of the heart muscle" but did not include this in phrasing the law of the heart. I would suggest therefore that in order to avoid ambiguity or misinterpretation the law of the heart be amended somewhat as follows:

"The law of the heart is thus the same as the law of muscular tissue generally, that the energy of contraction, however measured, is a function of the length of the muscle fiber" *under equivalent states of responsiveness.* Within recent years the operation of the law of initial length has seriously been questioned on the basis of studies of the human heart by catheterization technics.[36] We may predict with confidence that when we are able to overcome the technical difficulties that still impair the accuracy of pressure determinations in catheterization studies,[37] a careful evaluation of results will demonstrate the validity of the law of cardiac performance. However, I predict that complete assessment of the regulation of cardiac performance is not likely to succeed from analyses of hemodynamic data during health and disease alone, because innumerable variables are bound to be concerned. The multiple factors which can separately influence the response of the myocardium at equivalent initial lengths must be submitted to intensive experimental studies of a basic sort. A wide new field awaits exploration. Nothing would give

me greater pleasure than to attack the many facets of this interesting problem. However, since I am approaching the end of my experimental career I can perhaps best serve the cause of cardiac research in exhorting a new generation of investigators to accept the challenge of their execution.

Summary

Three classic discoveries—by Bowditch in 1869, by Howell and Donaldson in 1884, and by O. Frank in 1895—laid the foundation for the basic laws which govern the regulation of ventricular responses Years of further experimentation have not only shown that the mammalian heart operates according to these basic laws, but have also elucidated the many variables which sometimes obscure the evidence that these basic laws are important under normal and pathologic conditions.

In 1906, Y. Henderson evolved a law of uniformity of cardiac behavior which offered a geometric plan for roughly evaluating the relation of ventricular filling at different cycle lengths to systolic discharge and cardiac output; but his conclusion that the systolic discharge at any given heart rate cannot be increased above its normal value has not been supported by further studies.

In 1914 Straub and the writer independently reported experiments on mammalian hearts which appeared to show that the reactions of the mammalian ventricles to changes in venous return and arterial resistance harmonized with laws derived by Frank from studies on frogs' hearts. These experiments, like those of O. Frank, were unable to determine whether changes in presystolic pressure (initial tension) or volume (initial length) fundamentally regulate the degree of responsiveness, however measured. Shortly after the publication of these researches, Starling and his associates, on the basis of experiments on the heart-lung preparation which were highly suggestive but not quite conclusive, concluded that in the reaction of the heart to increased inflow and increased resistance, the only factor which constantly varies with the response of the ventricles is the volume of the heart, that is, the length of its muscle fibers. The law of the heart was thus reduced to the formula that "the mechanical energy set free on passage from the resting to the constricted state depends on the area of 'chemically active surfaces,' i.e., on the length of the muscle fibers." This basic concept has subsequently been validated by nearly all investigators.

In 1922 the writer and Katz delineated the detailed changes in the patterns of ventricular filling and emptying occasioned by alterations in venous return, arterial resistance and heart rate, and analyzed their relation to presystolic ventricular volume. It was concluded that Starling's interpretations required some modification. For instance, the rate and degree of ventricular filling are a resultant of the atrioventricular pressure gradient, the variable effect of atrial systole, and the time interval available for ventricular filling. Furthermore, these and subsequent studies by the writer have revealed that while the mode, duration, and extent of ventricular emptying are in a measure determined by the presystolic size, primary factors which affect the responsiveness of the myocardium are likewise of great importance. These include such factors as coronary blood supply, humoral agents, and nervous actions on the ventricular muscle.

It is suggested that the operation of the law of initial length will also be found valid in the human heart under equivalent states of myocardial responsiveness.

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The Relief of Acute Right Ventricular Strain by the Production of an Interatrial Septal Defect

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Since sudden resistance increase in the pulmonary circulation leads to right ventricular overdistension and subsequent failure, the question was studied whether or not the existence of an experimentally produced interatrial septal defect could prevent an overstretching of the right myocardium in acute pulmonary stenosis. It was found that myocardial overdistention could be prevented by a small interatrial septal perforation without essentially changing normal interatrial pressure relations. A large defect, which also protected the right heart muscle from overstretching, changed atrial pressure relations and cardiac dynamics entirely.

IN patients with a patent foramen ovale unoxygenated blood may enter the systemic circulation when the usual left to right interatrial pressure gradient is reversed. In animals with experimental interatrial septal defects, right atrial pressure exceeded left (a) occasionally during atrial systole, (b) consistently during inspiration[1] and (c) for a longer period during right ventricular failure due to infusion of large amounts of fluid.[2] The frequent clinical occurrence of right to left shunts and right heart strain due to increased pulmonary resistance warranted further investigation of the basic dynamic changes in conditions which bring about a reversal of the interatrial pressure gradient. Pulmonary stenosis, known to increase right atrial pressure and to produce right ventricular failure[3] was therefore used to study left and right atrial, right intraventricular and aortic pressures in *one and the same* animal first before and then after the production of an interatrial septal defect.

METHOD

Eleven dogs weighing between 11 and 18 Kg. were anesthetized with 3 mg. per Kg. of morphine sulfate followed by intravenous injection of 200 mg. per Kg. sodium barbital. The chest was opened through the anterior midline. Adequate artificial respiration was maintained, and was interrupted for brief periods when records were taken. The pulmonary artery was dissected free at the conus and a metal clamp applied. The clamp had a lower stationary arm upon which the vessel rested and an upper movable arm for finely graded compression by means of a micrometer screw arrangement on the handle. The clamp was firmly fixed so as to maintain its position for *accurately reproducible* degrees of constriction *before* and *after* the production of an interatrial septal defect. The degree of constriction was changed stepwise, thus always permitting a stabilization of the circulation from one step to the next. To prevent clotting of cannulas, 20 mg. of heparin were administered prior to cannulation. Aortic pressure pulses were obtained by introducing a rigid cannula through the left carotid artery. Left atrial pressures were recorded through a short catheter of 2.5 mm. lumen through the largest pulmonary vein of the left upper lobe and right atrial pressures were obtained through a 5 mm. wide sound passed through the right jugular vein. In two experiments right intraventricular pressure was recorded additionally with a 15 gage needle thrust through the right ventricular wall. All cannulas were fixed to reduce extraneous vibrations.

The pressure pulses were recorded with Gregg optical manometers and each beam was calibrated at the end of each record with a known static pressure in relation to a base line. A complete calibration of all manometers over the entire pressure range was made after each experiment. The atrial manometers were calibrated in millimeters of saline and the aortic and right ventricular manometer in millimeters of mercury. The common reference point for all pressures, the zero level, was set at the level of the animal board. Therefore all pressures are relative.

Interatrial septal defects were produced by two different methods. In some experiments a modified long hemostat was introduced through the tip of the

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left auricular appendage and thrust through the fibrous septum followed by a digital widening of the lesion by exerting pressure on the defect from the right atrial wall. In other experiments the defect was directly produced digitally by entering the left atrium through the left auricular appendage. Larger defects were produced by the latter method. Following the production of the lesion by either method the animals remained in good condition, as indicated by normal contours of the aortic pressure pulses. The postmortem examination and measurement of the defects showed that their sizes varied from 4 to 24 mm. in diameter. The lesions were round or oval and located in the fibrous part and, in the case of larger defects, also in the bordering muscular portion of the interatrial septum.

Both atrial pressure curves were analyzed at four points of special significance, the beginning of atrial systole, peak of atrial systole, end of atrial systole (Z point) which furnishes an index of initial tension within the ventricle, and finally the point just prior to the opening of the atrioventricular valves (V point) which serves as an index of atrial filling during ventricular systole.[4]

Results

Figure 1 shows two sections of a typical record of left and right atrial and aortic pressure pulses in an animal with an *intact septum* (A) before and (B) during moderate pulmonary artery occlusion. It is noted that left atrial pressure decreased with pulmonary stenosis and flattened out its pulse contour. Simultaneously right atrial pressure increased and its pulse contour became more prominent. Left-right atrial pressure relations were particularly determined by the alterations of the pulse contour.

These alterations were analyzed in all experiments by measuring instantaneous left and right atrial pressures at the beginning, peak and end of atrial systole and the V point. Data of two experiments are shown as examples in the four left columns (A) of tables 1 and 2. With pulmonary stenosis left atrial pressure declined more at the V point and peak of atrial systole than at the beginning and end of atrial systole (tables 1*A* and 2*A*, lines 1 and 4). On the other hand, right atrial pressure increased more at the V point than at the beginning of atrial systole (tables 1*A* and 2*A*, lines 2 and 5). These changes determined the left to right atrial pressure differences at different parts of the atrial cycle. The difference was calculated by subtracting right from left atrial pressures. During control the left to right atrial pressure difference was greatest at the V point and smallest at the peak of atrial systole (tables

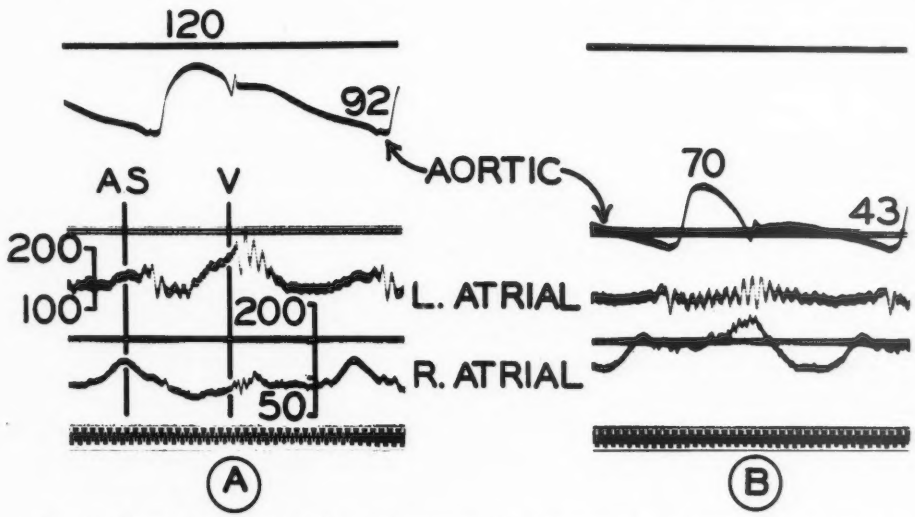

FIG. 1. Changes of left and right atrial pressures during progressive pulmonary artery constriction. *A*, control; *B*, moderate constriction. Calibrations in mm. Hg for aortic, in mm. saline for atrial pressure; zero point 60 mm. below level of atria.

1*A* and 2*A*, line 3). With pulmonary artery constriction right atrial pressure exceeded left during part of the atrial cycle with a maximal pressure reversal at the V point, while right pressure remained below left at the beginning (tables 1*A* and 2*A*, line 6), and in some experiments also at the end of atrial systole (table 1*A*, line 6). This pattern of a *phasic pressure reversal* in each atrial cycle was found in all experiments when the pulmonary artery was constricted by about 65 to 80 per cent of its lumen. With still greater degrees of pulmonary stenosis left atrial pulse contours became entirely obliterated, right contours indicated tricuspid regurgitation and right pressures exceeded left at all points of the atrial cycle.

When a *small* interatrial septal defect of 4 to 10 mm. in diameter was created in four dogs left atrial pressure decreased and right increased but slightly. As an example, the atrial pressure measurements of one of these experiments are tabulated in the four right columns of table 1*B*. When identical degrees of pulmonary artery constriction were applied as before the perforation, left atrial pressure decreased, right increased and both atrial pulse

TABLE 1.—*Influence of Moderate Pulmonary Stenosis on Interatrial Pressure Relations (A) before and (B) after the Creation of a Small Interatrial Septal Defect 5 Mm. in Diameter*

Point of measurement	A With intact septum				B With perforated septum			
	BAS	PAS	Z	V	BAS	PAS	Z	V
Without pulmonary artery obstruction								
(1) Left atrial pressure	148	162	156	168	143	165	160	185
(2) Right atrial pressure	112	130	112	130	110	142	139	135
(3) Left/right pressure difference	+36	+32	+44	+58	+33	+23	+21	+50
With identical degrees of pulmonary artery constriction								
(4) Left atrial pressure	139	146	143	156	135	150	146	152
(5) Right atrial pressure	130	160	135	184	110	160	130	158
(6) Left/right pressure difference	+9	−14	+8	−28	+25	−10	+16	−6

BAS = beginning of atrial systole; PAS = peak of atrial systole; Z = end of atrial systole; V = point before opening of atrioventricular valves. Left to right pressure difference is labeled *plus* and right to left *minus*.

TABLE 2.—*Influence of Moderate Pulmonary Stenosis on Interatrial Pressure Relations (A) before and (B) after the Creation of a Large Interatrial Septal Defect of 24 Mm. in Diameter*

Point of measurement	A With intact septum				B With perforated septum			
	BAS	PAS	Z	V	BAS	PAS	Z	V
Without pulmonary artery obstruction								
(1) Left atrial pressure	120	128	124	160	108	125	115	140
(2) Right atrial pressure	98	114	108	108	100	120	100	115
(3) Left/right pressure difference	+22	+14	+15	+52	+8	+5	+15	+25
With identical degrees of pulmonary artery constriction								
(4) Left atrial pressure	105	110	111	120	106	120	105	150
(5) Right atrial pressure	101	138	130	170	104	125	105	150
(6) Left/right pressure difference	+4	−28	−19	−50	+2	−5	0	0

BAS = beginning of atrial systole; PAS = peak of atrial systole; Z = end of atrial systole; V = point before opening of atrioventricular valves. Left to right pressure difference is labeled *plus*, and right to left *minus*.

contours changed about in the same manner but *not quite to the same extent* as with the intact septum. Thus the magnitude of the interatrial pressure gradient reversal was reduced by the small shunt (tables 1*A* and *B*, lines 4 to 6). The pattern of the phasic pressure reversal obtained with 65 to 80 per cent pulmonary artery constriction was, however, essentially the same as before the septum was perforated. According to the prevailing pressure gradient the flow through the shunt was, therefore, directed from left to right during some parts of the atrial cycle and reversed during other parts of the cycle. Greater pulmonary stenosis caused a complete interatrial pressure gradient reversal at all points of the atrial cycle. Even with severe degrees of pulmonary artery constriction left atrial pulse contours were, however, not quite obliterated (see also fig. 3*B*).

The influence of a *small* defect on directional atrial pressure gradients in another experiment is illustrated in the upper graphs of figure 2 by plotting left (solid line) and right (dotted lines) atrial pressures, measured at the V point, with the same degree of pulmonary stenosis before (*A*) and after (*B*) the defect was made. It is obvious from the crossing of lines that with the presence of a defect a greater degree of pulmonary artery constriction had to be applied to reverse the interatrial pressure gradient.

Figure 3 illustrates the typical difference of the response of the right heart when the septum was intact (*A*) and perforated (*B*) by a small fenestra 5 mm. in diameter. In the records of section *A* presystolic pressure in the right ventricle rose to 13 mm. Hg and the pressure rose very slowly to a systolic peak of only 27 mm. Hg. Right heart failure due to myocardial overdistention was obviously imminent. The records of section *B* show a reduction in presystolic pressure to 4 mm. Hg which was followed by a sharp elevation of pressure to a systolic peak of 58 mm. Hg. Duration of systole also increased. Obviously the presence of a *small* interatrial perforation served to relieve the right myocardium from augmented pulmonary resistance and aided in the prevention of right heart failure. The beneficial effect of such a shunt is also shown by the improvement of left ventricular output as evidenced by an increase in aortic pressure from 20/18 to 63/42 mm. Hg under identical degrees of pulmonary artery constriction.

Quite different results were obtained in those experiments in which a *large* interatrial septal defect was created. In seven dogs perforations varying from 14 to 24 mm. in diameter were made. Left atrial pressure decreased and right increased after the operation, thus reducing the right-left interatrial pressure difference (table 2*A* and *B*, lines 1 to 3). With identical

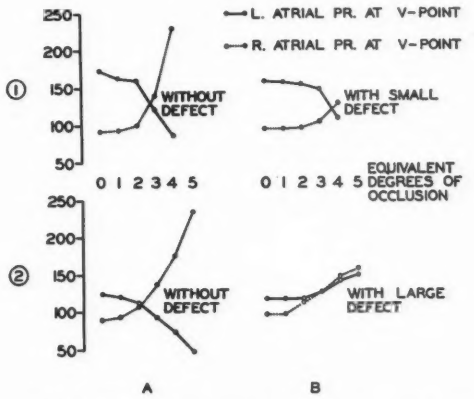

FIG. 2. Effect of pulmonary artery stenosis upon left and right atrial pressures when identical degrees of occlusion were applied before and after the production of an interatrial septal defect. Upper plots: one experiment with a small defect 5 mm. in diameter. Lower plots: another experiment with a large defect 24 mm. in diameter. Calibration in mm. saline, zero point 60 mm. below atrial level.

degrees of pulmonary artery resistance, left atrial pressure did *not* decline but even increased to almost the same level as the moderately rising right atrial pressures (compare table 2*A* and *B*, lines 4 to 6). In the lower graphs of figure 2 data of another experiment with a large defect were plotted. Here also left atrial pressure, measured at the V point (solid line), increased almost to the same extent as right (dotted line). Even with complete pulmonary artery occlusion (at stage 5 in figure 2) the magnitude of the interatrial pressure gradient reversal remained small. The data of table 2*B* and the lower right graph in figure 3 show that a large perforation tends to equalize both atrial

pressures at normal as well as with increased pulmonary resistance. This tendency is also illustrated in figure 4*A* and *B* by the records of (fig. 4*A*). Then the pulmonary artery was *completely occluded for half a minute* and the records reproduced in the right section of figure 4 were

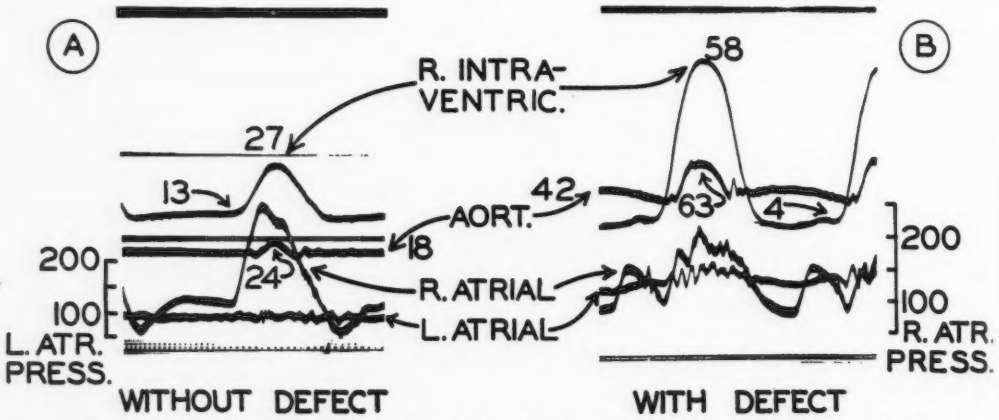

FIG. 3. Effect of a small interatrial septal defect 5 mm. in diameter upon right intraventricular, aortic, left and right atrial pressure when identical degrees of pulmonary artery constriction were applied in the same experiment (*A*) before and (*B*) after the perforation was made. Calibrations in mm. Hg for aortic and right intraventricular, in mm. saline for atrial pressures; zero point 60 mm. below level of atria.

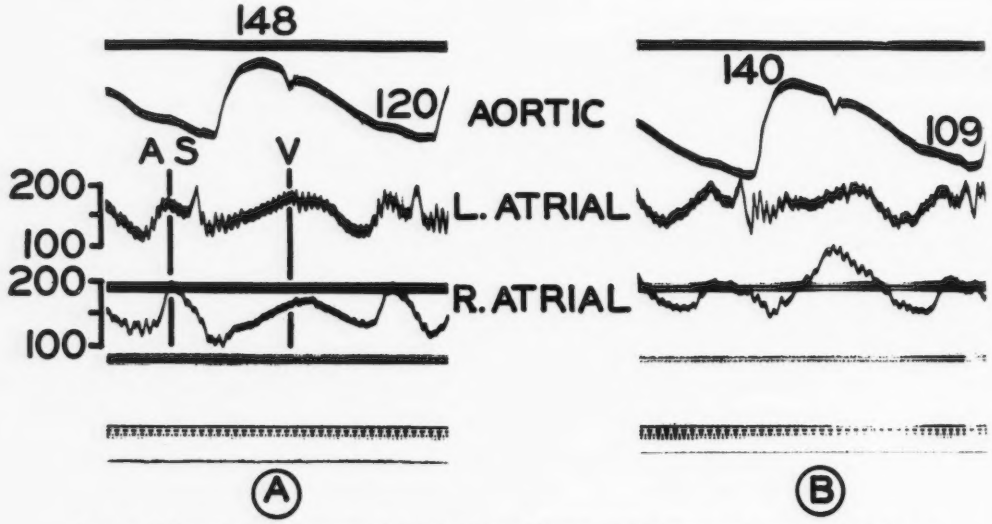

FIG. 4. Effect of a large interatrial septal defect of 23 mm. in diameter upon aortic, left and right atrial pressures (*A*) without pulmonary stenosis, and (*B*) with complete occlusion of the pulmonary artery for half a minute. Calibrations as in figure 1.

still another experiment. As soon as the large defect was created right and left atrial pulse contours became almost identical in appearance obtained. Right and left atrial pressures both increased and almost retained their previous contours while aortic pressures were barely

reduced. Accordingly the flow through the shunt was large enough to maintain a nearly normal cardiac output.

Discussion

The "zone of interatrial pressure reversals" which we were able to produce in our experiments by moderate pulmonary artery constriction emphasizes the importance of the recording of *phasic* atrial pressure changes for evaluating the interatrial pressure relations. Recording of mean pressures could not reveal these phasic pressure gradient reversals but could create the misleading picture that one atrial pressure was higher than the other during the entire atrial cycle. It ignores the fact that blood could be transferred through the shunt in opposite directions in rapid alternation during each atrial cycle. Phasic reversals of the interatrial pressure gradient and shunt flow of the nature reported in these experiments and such as those caused by respiratory changes[1] are apparently more frequently occurring than the conventional methods of testing reveal.

Comparison of the animals with different sized defects showed that atrial pressure relations were only slightly altered by the presence of a *small* defect. However, in acute pulmonary stenosis enough blood was shunted through such a small defect from the right to the left atrium to relieve right myocardial overdistention. The small shunt acted, thus, as a "failure-preventing safety valve." The experimental evidence presented here supports recent clinical observations reported by Engle and Taussig[5] that "the patency of the foramen ovale acts for a time as an 'escape valve' and lessens the load on the right side of the heart by the shunt of blood from the right auricle to the left."

A different situation was found in animals with large-sized defects. When the size of the defect exceeded 1.5 or 2 cm. in diameter in a medium-sized dog heart, atrial dynamics were completely altered (lower right plot in fig. 2). Of particular significance was the resemblance of right and left atrial pulse contours (fig. 4), indicating that the normally quite different atrial volume elasticity characteristics[6] were almost lost. We must assume that atria with such extensive septal defects form functionally a more or less common cavity.

Since a small septal perforation did not essentially alter atrial dynamics and limited the shunting of venous blood into the systemic circulation, right ventricular strain may be benefited by such a small shunt. No benefit could be expected, however, from large defects which change atrial dynamics extensively and permit the shunting of such large amounts of blood that cardiac output can be maintained near normal with complete occlusion of the pulmonary artery.

Summary

During acute experiments in open chest dogs the pulmonary artery was constricted with increasing severity by identical degrees of occlusion, first before and then after an interatrial septal defect was made. Instantaneous right and left atrial, right intraventricular, and aortic pressures were recorded through cannulas which were not displaced during the defect operation. Progressive pulmonary stenosis reduced left and increased right atrial pressures. Left atrial pulse contours flattened out and right became more pronounced. Moderate stenosis reversed the usual left to right interatrial pressure gradient at the peak of atrial systole and V point, whereas no pressure reversal took place at the beginning of atrial systole. The same type of phasic pressure reversals occurred after the creation of a *small* interatrial septal defect. Accordingly the shunt flow was directed from left to right during one part of the atrial cycle and in the opposite direction during the other part of the cycle. With marked stenosis right atrial pressures exceeded left at all points of the atrial cycle. Right heart failure produced in the intact heart by severe pulmonary artery constriction was alleviated by the presence of a *small* interatrial septal defect. The defect reduced excessive right intraventricular diastolic pressures and thus prevented myocardial overstretch. A *large* defect altered atrial dynamics insofar as left atrial pressures increased together with right when the pulmonary artery was occluded.

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Recommendations for Human Blood Pressure Determinations by Sphygmomanometers

By James Bordley, III, M.D., Charles A. R. Connor, M.D., W. F. Hamilton, M.D., William J. Kerr, M.D., and Carl J. Wiggers, M.D.

IT SHOULD be clearly recognized that arterial pressures cannot be measured with precision by means of sphygmomanometers. Direct registration of pressures by calibrated intra-arterial manometers has shown (1) that even during quiet breathing and slight sinus arrhythmia, systolic and diastolic pressures vary from beat to beat by several mm. Hg, and that these differences are greatly intensified during states of arrhythmia and deep breathing; (2) that auscultatory systolic readings from the brachial artery average 3 or 4 mm. Hg too low and show average scatter of ±8 mm. Hg; and (3) that auscultatory diastolic pressures taken at the point of dulling of the sounds average about 8 mm. Hg too high. The errors of clinical measurement of blood pressure can be summarized by saying that in normal persons a mean error of ±8 mm. Hg may be expected in individual readings of systolic and diastolic pressures. Despite this, clinical blood pressure determinations have proved very serviceable for practicing physicians, clinicians, insurance carriers, and others concerned with physical examinations, diagnosis, prognosis, or therapy. It is important, however, that any basic deficiency of sphygmomanometry be not increased by additional errors due to apparatus or technic.

The following recommendations have been drawn up with the idea of aiding examiners to avoid pitfalls and, as far as possible, to establish greater reliability and uniformity in measuring systolic and diastolic pressures.

The authors constituted the Committee to Revise "Standardization of High Blood Pressure Readings." This Committee, whose Chairman was Dr. Carl J. Wiggers, functioned under the auspices of the Council for High Blood Pressure Research of the Scientific Council of the American Heart Association.

These recommendations are being presented simultaneously in Circulation and in the Journal of the American Medical Association.

Apparatus

A sphygmomanometer consists of (1) a compression bag surrounded by an unyielding cuff for application of an extra-arterial pressure, (2) a manometer by which the applied pressure is read, (3) an inflating bulb, pump, or other device by which pressure is created in the system, and (4) a variable, controllable exhaust by which the system can be deflated either gradually or rapidly.

In the selection and maintenance of an instrument attention must be given to accuracy of construction and performance.

I. Mercurial types of manometers should be provided with a device to prevent spilling of the mercury when not in use. The zero level of the mercury should be easy to check and the scale should accurately indicate differences between the levels of mercury in the tube and the reservoir. Construction of the manometer should be such that the tubes and mercury can be cleaned without too much difficulty.

II. In the case of aneroid manometers, the readings on the dial at different pressures should check with those of a properly constructed and perfectly functioning mercury manometer. The fact that the pointer indicates zero may be no guarantee of accuracy over the whole pressure range. When placed and held under pressure for some time the pointer should not shift or creep.

III. The inflatable bag should, roughly speaking, be 20 per cent wider than the diameter of the arm or thigh on which it is to be used. Bags having the following widths are commercially available: for thighs of adults, 18 cm. (appendix VI); for arms of adults, 12 cm.; for children under 8 years, 8 or 9 cm.; under 4 years, 5 or 6 cm.; under one year, 2.5 cm. or less. A length of bag sufficient to half-encircle

a limb is adequate provided care is taken by the operator to place it on the side of the compressible artery. However, some authorities believe that any risk of misapplication should be obviated by use of a bag that nearly or completely encircles a limb.

The bag should be covered by a cuff of inextensible material of such a nature that an even pressure is exerted throughout the width of the cuff which lies over the artery. The cuff should have a convenient device for securely fastening after it has been applied to a limb. The cuff and its locking mechanism should be so constructed that inflation of the bag causes neither bulging nor displacement. There is no good evidence that any of several fastening devices featured by different manufacturers enhances the accuracy of pressure readings. Choice depends on personal ideas of convenience and manufacturers are to be commended on their improvement on the old fastening by a tapered cloth.

IV. Instruments in use should be checked frequently for significant leaks in pressure tubing and the compression bag, and competent, smooth functioning of the bulb exhaust and valves. Mercury manometers should be inspected often for loss of mercury, which leads to displacement of zero levels, and for dirty tubes and oxidation of mercury, which causes formation of a poor meniscus and clogging of air vents at the top of manometer tubes. Old leather filter discs should be replaced with ones of proper porosity as supplied by manufacturers.

Technic

I. *The Patient.* The patient may be either in a recumbent position or comfortably seated. The patient should be placed at ease and time should be allowed for recovery from any unusual recent exercise, meals, or apprehension. The arm should be bared, slightly flexed, abducted, and perfectly relaxed. In the sitting position the forearm should be supported at heart level on a smooth surface. The hand may be pronated or supinated later, depending on which position is found to yield the clearest sounds. The deflated bag and cuff should be applied evenly and snugly around the arm with the lower edge about 1 inch above the antecubital space. If the veins of the forearm are prominently filled or there is evidence of congestion the cuff should be applied while the arm is elevated in order to promote venous drainage.

II. *General Precautions.* The mercury column must be vertical. The meniscus should be read at a level with the observer's eye. It is not important to place the manometer at the heart level. The sounds heard on auscultation are not heart sounds; some misconception regarding this still exists.

III. *Determination of Systolic Pressure by the Palpatory Method.* A comparison of systolic pressure by the palpatory and auscultatory method is always advisable except in infants in which the former method alone may be feasible. Since it is impossible for an individual to make simultaneous readings by the two methods unless a bracelet form of stethoscope receiver is used, a preliminary determination of systolic pressure by the palpatory method is advantageous. Such observations reassure the patient and offer the examiner a rough idea as to the maximum pressure to which the system needs to be elevated in subsequent determinations.

The patient's radial pulse should be palpated and its rate and regularity estimated and recorded. The pressure of the system should be raised to a level about 30 mm. Hg over the point at which the radial pulse disappears. Pressure should then be released slowly from the system at such a rate that pressure in the manometer falls about 2 to 3 mm. Hg per heart beat. (See appendix I.) The return of palpable beats at the normal rate of the heart should be noted as a preliminary estimate of systolic pressure. The cuff should be rapidly and completely deflated before further determinations are made. The whole procedure should be carried out as quickly as is consistent with accurate determinations.

IV. *Determination of Systolic Pressure by the Auscultatory Method.* A stethoscope receiver should be applied snugly over the artery in the antecubital space, free from contact with the cuff. (See appendix II*A*.) The pressure in the sphygmomanometer should then be raised rapidly and decreased slowly, as in the palpatory

method, until a sound is heard with each heart beat. Note the reading as systolic pressure.

As a rule, systolic pressure determined by the auscultatory method is higher than the pressure at which radial pulse beats are first palpable. In case the palpatory reading should be higher than the auscultatory, a number of maneuvers may be undertaken to improve conditions for hearing the sounds. (See appendix II *B*.) If, despite such efforts, the pressure read by palpation continues to be higher, it should be accepted as the reading for systolic pressure. This should be noted.

V. *Determination of Diastolic Pressure by the Auscultatory Method.* With continued deflation of the system below systolic pressure at a rate of 2 to 3 mm. Hg per heart beat the sounds undergo changes in intensity and quality. As the cuff pressure approaches diastolic the sounds often become dull and muffled quite suddenly and finally cease. It appears that the point of complete cessation is the best index of diastolic pressure. (See appendix III.) Under hemodynamic conditions in which no cessation of sounds occurs, the point of muffling should be taken as diastolic pressure, if distinctly heard, and should be recorded as the point of muffled sounds. When no clear demarcation of the muffling is heard, diastolic pressure should be left indefinite and so indicated, for example, 150/30?

VI. *The Operator.* A number of consecutive determinations of systolic and diastolic pressure should be made and, if they agree reasonably well, the average should be taken. Variations in auditory acuity are important. A physician aware of defective hearing should use an amplifying stethoscope. Auditory acuity is of importance in subtler ways. The first sounds that occur at systolic cuff pressures and the last ones to occur in determinations of diastolic pressure are exceedingly feeble and of short duration. Physicians improve their acuity by training, but personnel to whom blood pressure determinations are often relegated do not have equivalent auscultatory experience.

Appendix

I. The rate of pressure fall suggested is not only convenient in detecting the precise cuff pressures at which sound phenomena occur but, in the case of portable mercurial manometers commonly employed, it should not be faster. Many mercurial sphygmomanometers contain a porous covering over the manometer tube to prevent spilling of mercury when folded into a case. This reduces the rate of air flow through the porous covering which tends to develop a negative pressure above the mercury column and prevents equalization of pressure with the cuff when the mercury column drops too fast. On the other hand, too slow a release of pressure tends to cause intermittent trapping of blood between systolic and diastolic levels.

II. The following maneuvers are often helpful in improving the distinctness and quality of sounds:

(A) Slight variations in pressure and shifts in the position of the stethoscope receiver. Firm application of the receiver often facilitates recognition of the first sounds in determination of systolic pressure; but compression of the artery by a receiver must be avoided in determination of diastolic pressure. Occasionally better sounds are heard on the upper arm just above the antecubital space (owing to existence of aberrant arteries (?)).

(B) Avoidance of congestion in arm veins. Congestion stultifies the auscultatory criteria both by lowering the level at which sounds appear and by causing them to drop out when the cuff pressure is between systolic and diastolic (auscultatory gap). Clothing should be adjusted to avoid constriction and the cuff should not be inflated when the arm is pendant. If there is any sign of the auscultatory gap the observation should be repeated by filling the cuff when the arm is upraised.

III. The recommendations formulated in 1939 contained the suggestion that two values for diastolic pressure be recorded; for example, 140/80–70. It is the impression of the Committee that such a practice has not been followed very generally. It doubts, on the grounds of hemodynamics, the propriety of listing two figures as "diastolic pressure." The disappearance of auscultatory sounds as a criterion of diastolic pressure is recommended on the following grounds:

(A) The current practice of using the point

of sudden muffling of the sounds was based (1) on comparisons with oscillatory criteria, and (2) on hemodynamic data derived from studies of excised or isolated arteries undergoing direct compression or decompression. The former (1) is of dubious value since no general agreement has been reached regarding the oscillatory criteria of diastolic pressure. The latter (2) appears to be risky owing to the fact that unsolved physical factors may enter when pressure is transferred to arteries from a cuff of arbitrary size through the tissues of a limb.

(B) While some difficulties still exist in making absolute comparisons between pressures determined by optical manometers and those revealed by auscultatory criteria, a limited number of such comparisons strongly suggests that, on the average, the cessation of sounds conforms rather better to the intra-arterial diastolic pressure and that dulling of sounds appears 5 to 10 mm. Hg above this level.

(C) Accuracy, not applicability to every individual, should determine the choice of criteria. The fact that sounds may persist as cuff pressure is reduced to lower levels, or even to zero, in certain clinical states, such as aortic insufficiency, hyperthyroidism, anemia, and in an occasional normal person, should not determine the selection of an equivalent criterion for diastolic pressure if it is not exact. The fact remains that cessation of sounds *does occur* in a very large percentage of all individuals examined. It is therefore recommended that the less exact criterion of muffled sounds be used *only when necessary* and that such readings be recorded as the point of muffled sounds. If any significance is attached to the fact that sounds are heard below this point, it should be recorded.

(D) Tests of different examiners reveal that, probably owing to different degrees of auditory acuity, there is a greater uniformity in decisions as to when sounds cease than as to the point at which they begin to muffle. Hence greater uniformity in recording diastolic pressures and enhancement of their accuracy in any statistical study may be expected by using disappearance of sounds as a criterion. Furthermore, the distinctness or demarcation of the dulling phase varies in different subjects examined. Frankness must cause us to admit that all too frequently the reading of diastolic pressure by this criterion becomes merely a guess.

IV. *Arrhythmias and Dyspnea.* The determination of blood pressure in arrhythmias and in pulsus alternans is unsatisfactory at best. An occasional premature contraction can be ignored. When continued irregularity occurs, as in auricular fibrillation or coupled beats, or in cases of pulsus alternans, the readings at which sounds appear and disappear in the stronger and weaker beats should be recorded. A similar procedure may be followed in patients with dyspnea.

V. *Basal Blood Pressures.* When special studies of blood pressure are required, determinations should be made under basal conditions similar to those used in metabolic studies. A convenient way to accomplish this is to determine the patient's blood pressure before breakfast and before arising in the morning. Alternatively it may be made in the office 10 to 12 hours after a meal and after the patient has reclined for at least 30 minutes in a comfortably warm room.

VI. *Blood Pressure in Thighs.* Measuring the pressure in the thigh arteries poses difficulties that have not been solved. The exact cuff size for thighs of different size has never been worked out. In normal persons one guiding principle should be kept in mind, namely, systolic pressure in the thigh by intra-arterial measurement may be 10 to 40 mm. Hg higher than in the arm, but diastolic pressure is essentially the same. If one uses apparatus on a normal individual in which the thigh diastolic reading is higher than arm diastolic reading, the cuff width should not be trusted to give correct readings. In coarctation of the aorta, systolic pressure is very much lower and diastolic pressure a little lower in the thigh than in the arm. This cannot be truly recognized with a cuff that has not been tested carefully on a normal thigh of the same size as that of the patient.

VII. *Multiple Blood Pressure Determinations.* When anomalies of the large arteries are suspected or an unexplained hypertension exists in a brachial artery, pressure readings should be made in both arms and in one or both thighs.

It is suggested that the blood pressure of a new patient be taken in both arms.

Documentation

Brief summaries of the pertinent literature since 1930 upon which the foregoing recommendations were based are appended. Although Bazett's studies pertained largely to oscillatory criteria, his communications contain information of general applicability and are therefore included.

Bazett, H. C., and Laplace, L. B.: Studies on the Indirect Measurement of Blood Pressure. I. Sources of Error in Riva-Rocci Method. Am. J. Physiol. **103:** 48, 1933.

"A comparison of blood pressure measurements made simultaneously directly on the right femoral artery and indirectly by a modified Riva-Rocci method on the left thigh in dogs is described. Both records were made optically. The indirect oscillatory method was demonstrated to be accurate for end systolic pressure whether a single or double bag system was employed, provided that a clear criterion was demonstrable, and that the bags were of proper size and properly applied . . . A single bag or a double bag system should compress the thigh for a length of at least 12 cm. in dogs of 12 to 18 Kg. weight. In a double cuff system the upper bag must have a breadth of at least 5 cm. Cuffs of similar size are probably suitable for use on the human adult arm . . . Changes in blood pressure are produced by inflation of a cuff, partly from mechanical obstruction of a large area, partly through reflex adjustments to this obstruction. These changes rarely exceed 5 to 10 mm. with occlusion of the thigh in the dog; in man with occlusion of one arm the effects are probably less than this . . . During rapid deflation, profound local changes may occur in the pressures in the vessels previously compressed. Both lateral systolic and lateral diastolic pressures are reduced, probably as the result of absorption of pressure energy through the induction of a rapid velocity head into the empty vessels below the cuff. In consequence all measurements by indirect means of the lateral pressure levels are too low, unless the deflation is conducted slowly. Moderately slow deflation and consequent congestion do not introduce serious errors. Deflation at a rate of 2 or 3 mm. per second is recommended . . . Some values for differences between end and lateral pressures in the femoral artery of dogs are given: . . . The systolic difference with a pulse pressure of 52 mm. amounted, on the average, to 18 mm.; in the presence of aortic regurgitation with a pulse pressure of over 100 mm., to one of 20 to 40 mm. In diastole the end pressure might be 2 mm. below or 13 mm. above the lateral pressure; the mean value was 4 mm. above it."

Bazett, H. C., Laplace, L. B., and Scott, J. C.: The Pressure Changes Induced in the Vascular System as the Result of Compression of a Limb, and Their Effect on the Indirect Measurements of Lateral Pressures. Am. J. Physiol. **112:** 182, 1935.

"It has been shown in a schema, and also in dogs, that the process of compression of a segment of the vascular system by an air column alters the actual pressures within the system at compression pressures which exceed diastolic pressure. Diastolic pressure is raised particularly at pressures just above the diastolic level; systolic pressure is lowered at pressures below the systolic level, raised at pressures above it. At the true lateral systolic level these two effects more or less neutralize one another. The changes are shown to be modified by the volume of the compressed segment. The raising of diastolic pressure and lowering of systolic result from the decreased volume-elasticity coefficient created by the air column; the ultimate rise in systolic pressure depends on the stoppage of the flow and reflection of the primary wave; this second change is only brought gradually into action by an air compressing system, owing to the cushioning effect of the air column . . . The effects of compression on diastolic pressure may be very unequal in the two separated parts of the main system. When separation is effected, the pressure changes proceed independently in the two sections according to their own volume-elasticity coefficients and rates of outflow. The peripheral pulse pressure tends to be the greater owing to the lengthening of the diastolic period in this section, and the consequent fall of diastolic pressure to a lower level, but the whole picture may be altered by the direction in which the contents of the compressed segment are mainly discharged. In general this discharge is towards the side which has the slower rate of fall of pressure . . . The flow of fluid along the angles of compressed arteries is denied; fluid transmitted at compression pressures, which exceed the lateral systolic pressure, does so in the form of a wave of 'bolus' type."

von Bonsdorff, Bertel: Zur Methodik der Blutdruckmessung. Acta med. Scandinav. Suppl. LI, 1932).

Cubital pressure was recorded with the Broemser glass plate optical manometer from one arm, together with respiration, and estimated systolic and diastolic pressures on opposite arms by appearance of sound and cessation of pure sound quality. In 44 registrations of patients with various clinical disorders they found that systolic and diastolic pressure comparisons can correspond under some conditions. Very often, however, auscultatory readings are higher or lower than directly recorded pressures. The pulse pressure tends to be too low by the Korotkow method. Respiratory variations

of several mm. Hg occur during natural respiration; these become greater, the deeper and slower that respiration becomes . . . The following reasons are suggested for discrepancies:

"Under otherwise similar conditions pulse waves of different forms are suppressed with variable facility. In determining diastolic pressure by auscultatory methods the results are apt to be affected by the ability of the vascular system to undergo vibrations. Other technical errors obviously enter."

Hamilton, W. F., Woodbury, R. A., and Harper, H. T.: Physiologic Relations between Intrathoracic, Intraspinal, and Arterial Pressures. J.A.M.A. **107:** 853, 1936.

Thirty comparisons between intra-arterial pressures and pressure readings by the cuff method indicate that the indirect method is 3 to 4 mm. Hg too low in evaluating the brachial systolic pressure and 9 mm. Hg too high for diastolic pressure.

Woodbury, R. A., Robinow, M., and Hamilton, W. F.: Blood Pressure Studies on Infants. Am. J. Physiol. **122:** 472, 1938.

The use of the pediatricians cuff (4.5 cm. wide) gave palpatory readings 20 to 25 mm. Hg too low. (The auscultatory method cannot be used in infants.) Trying narrower cuffs, the authors could get agreement with direct intra-arterial recordings of the umbilical systolic pressure only when the cuff was 2.5 cm. wide. Comparisons were made in 37 newborn babies. Recent authors (quoted) have given values, using wide cuffs, that are lower (systolic) than mean pressures recorded by cannulating the umbilical artery.

Robinow, M., Hamilton, W. F., Woodbury, R. A., and Volpitto, P. P.: Accuracy of Clinical Determinations of Blood Pressure in Children. Am. J. Dis. Child. **58:** 102, 1939.

Since the cuff width is of importance in the reading of blood pressure in infants it was expected that cuffs as used in children might be either too wide or too narrow to give correct readings of systolic and diastolic pressure. The proper width of cuff increases with the circumference and with the length of the arm and probably decreases with its compressibility. All these factors vary in such a manner that the proper width of cuff increases with age. It is suggested that three cuffs be used for children. The average of 22 determinations in normal new babies was 1.3 mm. Hg lower than the average determination of umbilical systolic pressure. The average error of a single determination was 3.6 mm. Hg.

The 5 cm. cuff was used in 12 children less than 1 year old gave average figures that differed 0.3 mm. Hg from the average brachial systolic pressure. For diastolic pressure the average reading was 11 mm. Hg too high. The average error of a simple determination was ±6.5 mm. Hg systolic and ±11 mm. Hg diastolic.

The 9 cm. cuff gave in 34 children 1 to 13 years old a figure that was 2.1 mm. Hg (systolic) too low, and 4.6 mm. Hg (diastolic) too high. The average errors of a single determination were ±5.1 mm. Hg systolic and ±7.3 mm. Hg diastolic.

Either systolic or diastolic readings could be made to agree with direct measurement by choosing a proper cuff width. The same cuff width would not do for both pressures. Three widths above were chosen to give a reasonably close figure for readings of both systolic and diastolic pressures.

Berry, M. R.: The Mechanism and Prevention of Impairment of Auscultatory Sounds during Determination of Blood Pressure of Standing Patients. Proc. Staff Meet., Mayo Clinic **15:** 699, 1940.

"While he is determining blood pressures of standing patients by the usual auscultatory method, the physician frequently finds the auscultatory sounds to be very indistinct. Occasionally, sounds cannot be heard. Under these circumstances it will be difficult or even impossible to determine blood pressure. Such impairment of sounds seems to be referable to venous congestion distal to the cuff of the sphygmomanometer.

"If the arm of a standing patient is raised above his head until the veins are relatively empty, if the cuff of the sphygmomanometer is then inflated so that a value exceeding that of the systolic blood pressure is obtained, and if the patient's arm is then lowered, impairment of auscultatory sounds will be prevented and determination of such a patient's blood pressure will be simplified."

Ragan, Charles, and Bordley, James, III: Measurements of Blood Pressure. Bull. Johns Hopkins Hosp. **69:** 526, 1941.

"The commonly employed clinical method of measuring blood pressure should not be looked upon as a truly accurate procedure. In most adult subjects it provides reasonably reliable information, but in a significant number of cases the information may be quite misleading. Misinformation is particularly likely to be obtained in subjects with unusually large or unusually small arms; if the arm is small, the clinical estimate of the systolic pressure is likely to be too low; if the arm is large, the clinical estimate of both systolic and diastolic pressure is likely to be too high. The error in either direction may exceed 30 mm. Hg.

"The foregoing observations must be borne in mind whenever it is necessary to come to a decision concerning the diagnostic or prognostic significance of minor depressions or elevations in the level of the blood pressure. Statistical studies of the relation between blood pressure and body weight should take into account the influence of the circumference

of the arm upon the accuracy of the blood pressure measurements.

"ADDENDUM. *Note on the 'Auscultatory Gap'*. The phenomenon known as the 'auscultatory gap' which is noted at certain times and in certain patients during the measurement of arterial pressure by the usual auscultatory method has been recognized by clinicians for many years ... When the cuffs encircling the two arms were inflated rapidly so as to avoid venous congestion distal to the cuffs, no auscultatory gap occurred as the cuffs were subsequently deflated. On the other hand, when inflation was carried out gradually, a well-marked auscultatory gap was noted during deflation. A very striking difference may be noted between the intra-arterial pressure tracings in the two records. After rapid inflation of the cuffs the intra-arterial pressure fell some 45 mm. Hg below the diastolic pressure level in the unoccluded artery; as the cuffs were deflated, the intra-arterial pressure rose steadily but the diastolic pressure below the occluding cuff never rose appreciably above the diastolic level in the unoccluded artery. After the slow inflation of the cuffs the intra-arterial pressure did not fall so low, and as the cuffs were deflated the intra-arterial pressure rose rather rapidly and the diastolic pressure below the cuff reached a peak which was well above that of the diastolic pressure in the unoccluded artery.

"These observations are recorded here to note the fact that prolonged partial occlusion of the veins of the arm during the inflation of a blood pressure cuff affects the arterial as well as the venous pressure distal to the cuff. The effect upon the arterial pressure may be the determining factor in the production of the auscultatory gap."

Steele, J. Murray: Measurements of Arterial Pressure in Man. J. Mt. Sinai Hosp. **8:** 1049, 1941–42.

"Concerning the comparison of simultaneous measurements of arterial pressure obtained by direct intra-arterial manometry and by indirect auscultatory technique in 39 individuals, it may be said that: 1. Systolic pressure was underestimated in indirect measurement by about 10 mm. Hg. In the present study, the indirect pressure in the brachial was compared with the direct pressure in the radial artery. This procedure may account for half of this difference. 2. In auscultatory technique the disappearance of sound proved to be a more accurate measure of diastolic pressure than the sudden muffling. The former overestimated diastolic pressure by 8.8 mm. Hg, the latter by less than 1. 3. The indirect auscultatory method of estimating arterial pressure is, considering its convenience and simplicity, an unusually accurate bedside method."

Wilkins, Robert W., and Bradley, Stanley E.: Changes in Arterial and Venous Blood Pressure and Flow Distal to a Cuff Inflated on the Human Arm. Am. J. Physiol. **147:** 260, 1946.

"The effects of inflating a cuff upon arterial and venous pressures distally were studied by use of the Hamilton manometers. Of interest to our project was the observation that when cuffs were inflated to pressures between diastolic and systolic, and maintained at these pressures, the cuff isolated the distal tree intermittently and caused an elevation of diastolic pressure peripheral to the cuff. These observations would seem to stress the importance of not maintaining rising and falling cuff pressures in this zone for too long a period in routine determinations of blood pressure."

Kotte, J. Harold, Iglauer, Arnold, and McGuire, Johnson: Measurement of Arterial Blood Pressure in Arm and Leg. Am. Heart J. **28:** 489, 1944.

"1. The systolic blood pressure in the arm can be measured with reasonable accuracy in most subjects with normal pressure, hypertension, and aortic regurgitation by the ordinary arm cuff and auscultatory technique. 2. The brachial diastolic pressure, as measured by the ordinary cuff, is usually too high, especially in aortic regurgitation. 3. The femoral systolic blood pressure cannot be measured accurately with the ordinary 13 cm. cuff. A wider (15.5 cm.) cuff permits more accurate measurement of the femoral systolic pressure except in subjects with aortic regurgitation whose pressures cannot be measured accurately with either cuff. 4. Femoral diastolic pressures obtained with either cuff were grossly inaccurate in all subjects. 5. The difference between the blood pressure in the arm and leg in patients with aortic regurgitation is not so marked as is generally believed because the cuff, wide or narrow, does not allow true measurements of femoral pressure. Therefore, it is probable that no diagnostic value should be attributed to this sign."

A Study of the Central and Peripheral Arterial Pressure Pulse in Man

Correlation with Simultaneously Recorded Electrokymograms

By A. H. Salans, M.D., L. N. Katz, M.D., G. R. Graham, M.D., A. Gordon, M.D., E. I. Elisberg, M.D., and A. Gerber, M.D.

This communication describes and discusses the results obtained in studying central and peripheral arterial pressure pulses in man by means of retrograde aortic catheterization. The pressure pulse transformation and pulse transmission in the aorticobrachial system are presented and compared with comparable tracings reported in the dog. Several normal subjects and patients with hypertension, aortic regurgitation and coarctation of the aorta were studied. The genesis of the central pulse contour in aortic regurgitation is reconsidered. The changes in central pulse pressure, produced by the Valsalva-like maneuver, and ventricular premature systoles have been investigated, especially in their relationship to cycle length, end-diastolic volume and peripheral resistance. The technic of obtaining pulse pressure recordings by retrograde aortic catheterization is recommended for determining the location, size and dynamic significance of coarctation of the aorta. As an additional study, aortic densograms and border electrokymograms from the aortic arch and left ventricular border were correlated with simultaneously recorded central aortic pressure tracings.

CATHETERIZATION of the human aorta has been used recently for diagnostic purposes in retrograde angiocardiography.[1, 2] This experience prompted the study of cardiovascular hemodynamics by means of retrograde catheterization of the human aorta, a field which has been little explored. This report deals with some preliminary observations on the contour, transmission rate and transformation of the central aortic pressure pulse. As part of this investigation the central pressure pulse was correlated with the simultaneously recorded electrokymogram of the aorta.

Methods and Procedure

Simultaneous aortic catheterization and electrokymography were performed in patients for whom the information so gained was thought to be diagnostically important. They are listed in table 1 with their final clinical diagnosis: cases 2 and 3 were shown later not to have cardiovascular disease.

1. *Aortic Catheterization.* The brachial artery was identified just above the antecubital fossa; the skin overlying it was prepared in the usual fashion for sterile surgery and was anesthetized locally. Through a small transverse skin incision, the brachial artery and vein were identified and exposed by incising the lacertus fibrosus. The vessels were separated and two temporary No. 1 black silk loop ligatures placed around the artery about 1 cm. apart in such a manner that when the loose ends were elevated, the vessel was temporarily occluded. A test occlusion of the artery was then performed and signs of ischemia sought for peripherally. A longitudinal incision approximately 2 mm. in length was then made in the artery between the taut ligatures and a No. 4–6 French catheter was inserted into this opening. Hemostasis was completely maintained by means of the ligatures on the artery. Once in place the ligatures could be loosened, the artery sealing off the opening around the catheter. The catheter was then passed under constant fluoroscopic control into the arch of the aorta, its tip being oriented in a caudal direction. After withdrawal of the catheter at the end of the observations the incision was repaired, with the stay ligatures secure, using No. 00000 arterial silk as a simple, full thickness, continuous suture to obliterate the opening. Approximately four to six sutures were usually required for

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hemostasis. The stay ligatures were then removed and the skin closed. Penicillin was given over a 48 hour period postoperatively.

It was noted that the catheter passed more readily into the aorta when the left brachial artery was used. Following the procedure the radial pulse was permanently abolished in one case, moderately reduced in two, and only slightly reduced in the remaining four; in none of these cases was there any evidence of impaired circulation to the extremity. None of the seven cases exhibited any type of cardiac arrhythmia during the procedure, nor were there any untoward reactions.

2. *Electrokymography and Pulse Recording.* Records were obtained with the patient in the recumbent position holding his breath in midinspiration as in our other studies.[3, 4] Intraluminal pressures were recorded with an electromanometer.* The kymographic apparatus employed was essentially that developed by Henny and Boone[5] as modified by Luisada and co-workers[6] and Grossman and Tiger.[7]

Simultaneous recordings of lead II of the electrocardiogram, intra-arterial pressures and the electrokymogram were made with a four channel direct-writing polyoscillograph.*[4] The recording fidelity of the electrokymographic equipment has been described elsewhere.[8] The galvanometer response to a square wave input (damping 71 per cent critical) was 95 per cent complete in 0.01 second. The time lag of an impulse through the catheter at 37 C. has been found to be 0.015 second.[9] The electrokymograms were obtained with the slit of the pickup device positioned perpendicular to the border of the aorta and within 4 to 6 cm. of the catheter tip in recording border tracings. Densograms were recorded similarly, except that the slit was placed completely within the visible shadow of the aorta and parallel to the indwelling catheter.

Discussion of Results

A. *Contour of Pressure Pulses*

1. *Central Aortic Pressure Pulses.*† The normal pulse wave contour, a typical example of which (from case 2) is shown in figure 1, is essentially similar to that in the dog,[10] showing the three fundamental changes of gradient (at points 3, 4, 5). By analogy with the pulse curves in the dog, the small vibrations 1 and 2 may be considered to be due to the contracting auricles and the bulging of the aortic valves respectively. In support of this genesis of vibration 1 may be cited its constant relationship, whenever it appears, to the end of the P wave. Vibration 2, approximately 0.03 second in duration, is rather constant in appearance and immediately precedes the onset of the anacrotic limb. The deformation of the pulse contour at point 6 is probably the reflected dicrotic wave, and the form of the summit (point 4) may be due to a reflected wave superimposed upon the fundamental form.

In arterial hypertension, the characteristic contour seen is similar to that which occurs in the dog, with a high resistance systemic arterial circuit.[11] Figure 2*A* is the aortic pulse of a relatively mild hypertensive patient (case 6). Compared to the normotensive pulse contour it shows: (1) a much earlier change in gradient of the anacrotic limb; (2) a diminished plateau duration at the summit; (3) a more rapid collapse following the systolic peak; and (4) a steeper gradient in early diastole. These deviations from the normal contour vary directly with the elevation in blood pressure in the two cases of hypertension studied.

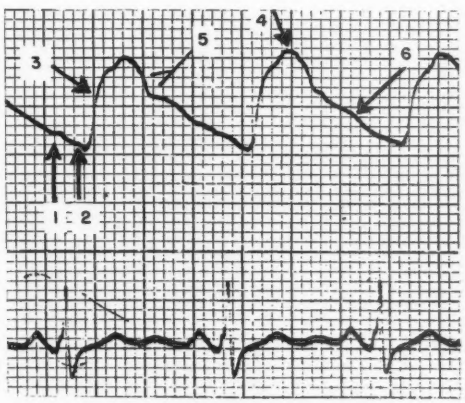

Fig. 1. Normal central aortic pressure pulse (case 2). Aortic pressure pulse curve above, lead II of electrocardiogram below, simultaneously recorded. Paper speed: 25 mm. per second. Time lines are 0.04 second apart. See text for discussion and meaning of numbered points.

In the patient with aortic regurgitation (case 7), when the central pressure pulse was recorded from the arch of the aorta (fig. 2*B*), the curves are essentially like those seen in the experimental animal.[12] There is a brief notch at point

* Sanborn Company.

† The pressure levels obtained in these cases are given in table 1.

1 on the anacrotic limb especially marked in the beat following a ventricular premature systole in figure 2*B* where it also occurs lower down on the curve. This early notch is also seen in experimental regurgitation.[12] The cause for this phenomenon may be an orifice relatively re-

evident. In figure 2*B* where a change in gradient (point 2) probably marks the end of the incisura, this collapse can be most readily seen. The pressure declines more gradually during the remainder of diastole (but more so than is seen experimentally). The ventricular prema-

TABLE 1.—*Central Aortic Blood Pressure in the Seven Cases Studied*

Case	Diagnosis	Age	Sex	Central Aortic Pressure (Average)	Brachial Artery Pressur (Cuff Method)
				mm. Hg	
1	Labile hypertension	32	female	135/70	120/70
2	Normal: no cardiovascular disease	29	female	110/75	115/75
3	Normal: no cardiovascular disease	31	male	120/65	110/70
4	Mild hypertension	53	female	155/100	160/90
5	Coaretation of the aorta	42	female	180/85	192/86
6	Essential hypertension. Arteriosclerotic heart disease	64	male	170/95	165/100
7	Aortic regurgitation	47	female	235/60	180/60

* Not recorded simultaneously with central aortic pressure.

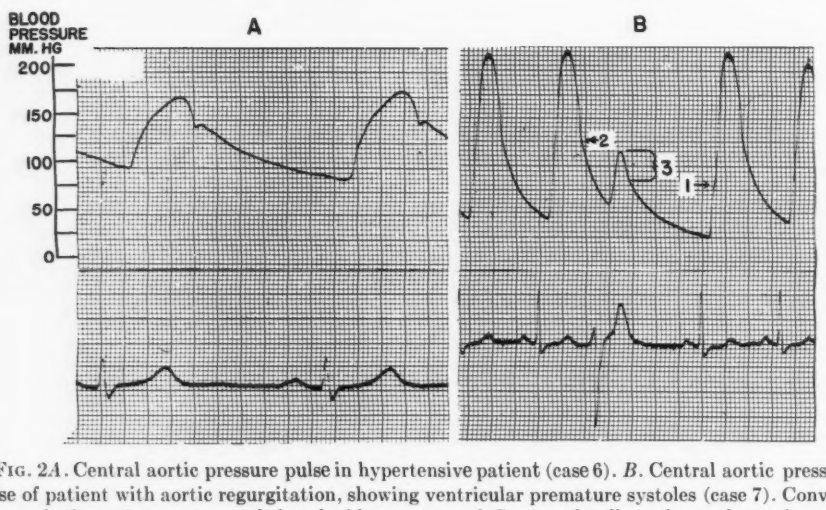

FIG. 2*A*. Central aortic pressure pulse in hypertensive patient (case 6). *B*. Central aortic pressure pulse of patient with aortic regurgitation, showing ventricular premature systoles (case 7). Conventions as in figure 1, except recorded at double paper speed. See text for discussion and meaning of 1, 2 and 3 in segment *B*.

stricted for the greatly increased systolic output. In aortic regurgitation the pulse shows a steep rise to an early and rather peaked summit, followed by a marked systolic collapse. In the absence of a clearly defined incisura, the beginning of diastole cannot be precisely determined, but the steep early diastolic collapse is

ture systoles in figure 2*B* show most clearly the continuous though gradual diastolic decline of pressure (to about 30 mm. Hg) following the systolic and early diastolic collapse. By analogy with records obtained experimentally in dogs with various degrees of regurgitation, the pulse contour in this case would indicate

a large leak, which was in confirmation of other clinical data.

Wiggers[11] has explained the rapid systolic collapse in aortic regurgitation as the consequence of a redistribution of ejection so that most of the blood is discharged during the first half of the ejection phase. In addition, he has emphasized that the high systolic pressure reached at the peak contributes to the sharp drop. In our patient, the almost identical, though miniature, contour of the pulse curve recorded in the ventricular premature systole (fig. 2*B*) is difficult to explain on the above basis, since it resembles the contour of the sinus beats closely. The anacrotic limb is less steep, the pulse pressure smaller, the systolic peak level lower, and it does not clearly show the anacrotic notch described (point 1, fig. 3). But the systolic (point 3, fig. 2*B*) and early diastolic collapse segments show a striking similarity to the corresponding portion of the sinus beat, with only slight differences in gradient. Since the absolute level of blood pressure and the initial ventricular volume (and hence the rate of ejection) of the premature contraction are decidely less than the sinus beat, and yet the rapid collapse occurs, factors other than, or in addition to, those postulated by Wiggers (in the animal) must be operative in its genesis.

When recordings were made in a patient with a coarctation of the aorta of mild degree (case 5, figs. 3*A* and 3*B*), several changes occurred in the form of the aortic pressure pulse both above and below the region of coarctation. Above the coarcted area, the pulse contour shows only minor changes from the normal which are probably due to hypertension. (Other effects of coarctation on the pulse contour which might be expected are absent, probably because of the mild degree of the stenosis.) Just beyond the area of coarctation the changes in pulse form (compare fig. 3*B* with fig. 3*A*) consist of: (1) a decidedly less steep anacrotic limb rising protractedly to a late summit; (2) a distinct vibration appearing less than halfway up the anacrotic limb; (3) coarse systolic vibrations of rather low frequency (about 50 per second) on and at the summit of the curve; (4) a slight diminution of the pulse pressure, the systolic pressure falling more than the diastolic. These alterations in the pressure pulse are similar to those seen beyond the stenosis in dogs in whom the aorta was narrowed just above the aortic ring.[13, 14] In these animal experiments the more marked the degree of stenosis, the sooner vibration 1 (fig. 3*B*) appeared on the anacrotic limb, the more reduced was the anacrotic gradient preceding the vibration, the smaller were the vibrations at the summit, and the more marked the systolic pressure drop, the diastolic level remaining essentially unchanged. Judging

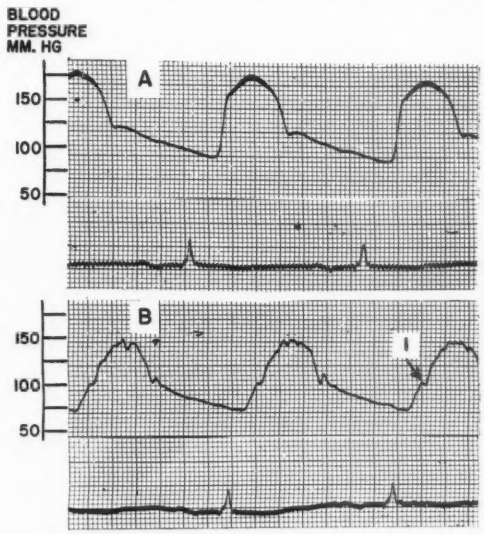

FIG. 3. Central aortic pressure pulse above (*A*) and below (*B*) the site of coarctation (case 5). *B* was recorded within a few seconds of *A*. Conventions as in figure 2. I in segment *B* indicates the anacrotic notch. Discussed in text.

by these criteria, the contour of the poststenotic pressure pulse indicates a narrowing of mild degree, a circumstance suspected on clinical grounds. The onset of the anacrotic limb of the poststenotic pulse curve precedes that recorded proximally by about 0.03 second. The pressure rise immediately following anacrotic halt coincides with the steep rise of the anacrotic limb of the prestenotic pressure pulse (as it is propagated peripherally). The mechanism responsible for the apparent accelerated onset of the poststenotic pulse wave is obscure, but may be related to the collateral circulation which enters below the stenosis. The dicrotic

notch becomes larger in amplitude and shorter in duration distal to the coarctation. The femoral pulse contour in human coarctation of the aorta has recently been studied.[15]

The recording of pressure pulses above and, if possible, below the site of coarctation can be used both qualitatively and quantitatively in the diagnosis of human coarctation, using the criteria discussed above to localize it precisely and determine its size and dynamic significance. This should provide more reliable data than routine methods now employed in the consideration of surgical intervention. It may also prove of value in determining the nature of hypertension encountered in this anomaly. The subject has recently been analyzed in detail by Gupta and Wiggers.[16]

2. *Valsalva Maneuver.* In two instances the central arterial pulse was recorded while the patient exhaled against a positive pressure of about 30 mm. Hg. Figure 4 shows representative sections from the beginning (strip 1), middle (strip 2) and end (strip 3) of the maneuver in one case. The blood pressure changed from 170/90 mm. Hg at the onset to 63/50 at the middle and 94/50 at the end of the maneuver. The ejection phases measure 0.27, 0.17 and 0.27 second for the corresponding cycles.* The cycle lengths in these instances are 0.80, 0.68 and 0.66 second, respectively. The contour of the pulse is altered decidedly during the Valsalva maneuver: the anacrotic limb begins 0.04 second later and rises less steeply; the summit is

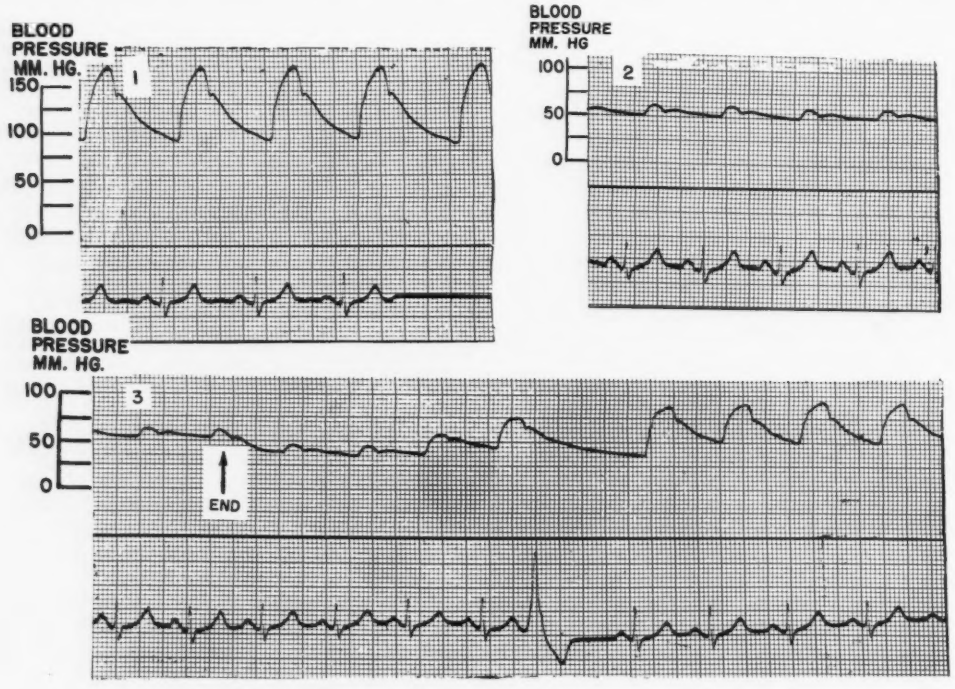

FIG. 4. Central aortic pulse tracing during Valsalva maneuver in case 6. Beginning, middle and end of maneuver are in segments 1, 2 and 3. Note electrocardiograph turned off before last pulse in segment 1. End of maneuver is marked in segment 3. Note ventricular premature systole with no evidence of its activity in the pulse tracing in segment 3. Conventions as in figure 1. Discussed in text.

* The ejection phase was measured from the beginning of the rise of the anacrotic limb to the end of the incisura. While this period includes the protodiastolic phase, it has a sharper definition and serves the purpose of a relative measure of change.

more flattened and a prominent dicrotic wave appears. The circulatory response to the Valsalva maneuver in various conditions is considered in detail elsewhere.[17]

3. *Premature Beats.* During the occurrence of ventricular premature systoles in the electrocardiogram, in case 6, the record of the pulse wave (fig. 5) illustrates several unusual circumstances: (1) mechanical evidence of the premature contraction is absent in the central pulse (see also fig. 6); (2) the ejection phase of the beat following the compensatory pause (that is, after a mechanical cycle length of 0.80 second) is almost identical with that of the normal cycle of 0.40 second (see below); (3) the systolic pressures during and the diastolic pressures at the end of the beats are almost identical whether the beat follows a double or a single cycle interval; (4) the dicrotic limb declines very gradually and continuously during the long pause, until the next mechanical systole. Unfortunately information about the ejection of the right side of the heart during the "dropped" mechanical beat of the left side is not available.

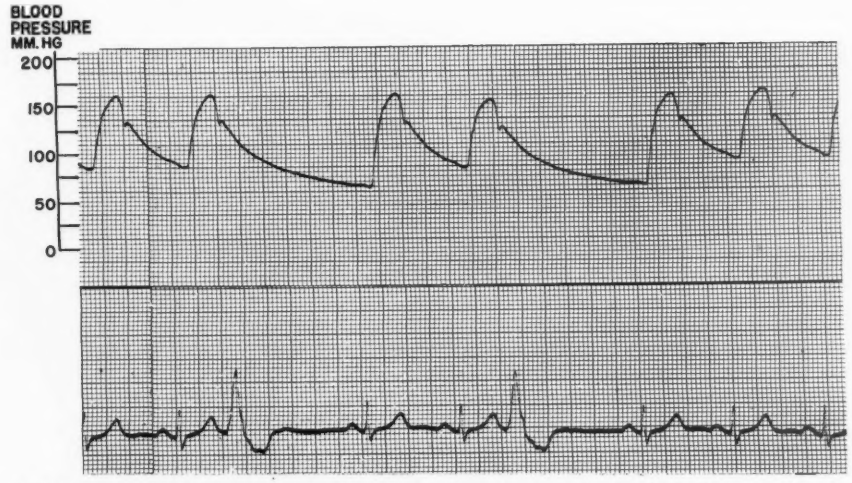

FIG. 5. Central aortic pressure pulse (case 6) showing absence of mechanical effect on pulse of ventricular premature systoles. Conventions as in figure 1. Discussed in text.

4. *Changes in Duration of Ejection Phase.* Based on detailed animal experiments, Wiggers and Katz[18] have described three primary influences on the ventricular ejection phase:

(a) Increased initial volume (without change in heart rate and blood pressure) prolongs the ejection phase.

(b) Increased resistance to emptying (constant heart rate and relatively unchanged controlled blood pressure), produced by clamping the aorta at the level of the diaphragm, results in a shorter ejection phase in normal hearts. They found that the hypodynamic heart subjected to increased resistance to its emptying

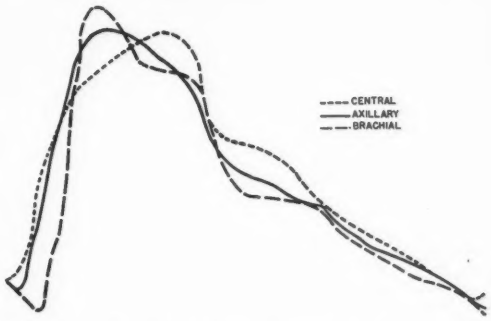

FIG. 6. Retracing of pressure pulses of case 3, recorded within 15 seconds of each other, from the central aorta (central), axillary (axilla) and brachial (brachial) arteries, superimposed in same time and pressure scales. Discussed in text.

could not increase the velocity of ejection so that the systolic discharge was reduced, diastolic distension increased and thus the ejection period ultimately actually lengthened.

(c) Heart rate leads to no definite and constant relationship between the duration of consecutive ejection periods and that of their preceding diastole. This last seems to hold true for the human heart also, at least on occasion (see fig. 7), inasmuch as the ejection phase is of the same duration during the normal cycle as it is following the compensatory pause during which the mechanical cycle is equal to twice the normal duration.

From the records of the Valsalva experiments it is seen that the length of the ejection phase varies *directly* with the height of the blood pressure. Though seemingly at variance with the experimental data in animals, it is explained by the fact that the blood pressure changes are determined by the filling of the left heart. Thus the reduced filling of the left heart causes a drop in blood pressure and at the same time by reducing the initial (end-diastolic) volume, shortens the ejection phase. As filling of the left ventricle increases again and contributes to the blood pressure rise, initial volume rises and the ejection phase is lengthened again in accordance with experimental data.

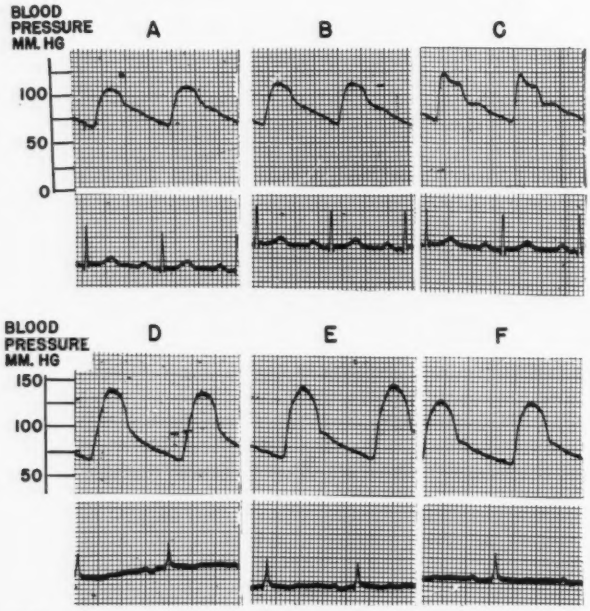

FIG. 7. *A*, *B* and *C* are pressure pulses recorded respectively from central aorta, axillary and brachial arteries in case 3, taken within 15 seconds of each other but at another time than those shown in figure 6. *C*, *D*, *E* and *F* are similar recordings respectively from central aorta, axillary and brachial arteries from case 5. Conventions as in figure 1. Discussed in text.

B. *Transmission of the Central Pulse to the Periphery*

The transmission time and velocity have been extensively investigated with volume pulses[19–22] and it has been found that the arterial pulse wave velocity varies directly with the rigidity of the arterial wall, traveling more slowly in progressing from the central (elastic) vessels to the peripheral (muscular) arteries. It also varies directly with the intravascular pressure and the degree of smooth muscle contractions of its wall.[11] However, data on pulse velocity in man from the aorta peripherally have been lacking.*

* While this manuscript was being prepared, an abstract appeared (T. G. Schnabel, W. J. Rashkind

Using the peak of the R wave of the electrocardiogram, measuring its distance from the rise of the anacrotic limb of the corresponding pressure pulse centrally and peripherally and dividing their difference by the distance measured with the indwelling catheter, the pulse velocity was calculated in three patients.* Table 2 gives the values obtained. The speeds found confirm the striking difference in pulse wave velocity in the central as contrasted with the peripheral blood vessels. Planimetry shows no significant change in mean pressure between the central and peripheral pulses in cases 3 and 5. In case 7, the central aortic and brachial artery pressure measurements (about 30 seconds apart) were quite different and there had been a marked reduction in mean pressure also; apparently a partial occlusion of the catheter had occurred in the interval.

C. *Transformation of the Central Pressure Pulse*

This has been extensively studied in the dog[10, 11, 21] ever since Otto Frank developed an adequate manometer with which he could give conclusive evidence for discrepancies in pulse form in different portions of the arterial tree.[23] We had occasion to observe the transformation of the intravascularly recorded central aortic pulse in the transmission to the brachial artery in four adult men. Figure 6 shows pressure pulse curves recorded from the arch of the aorta, the axillary artery and the brachial artery within 15 seconds of each other in a normal young adult, superimposed to utilize the same time and pressure scales. The surface areas of each of these curves are practically identical. In figure 7*A*, *B* and *C* are recorded curves from the same individual in the same areas at another time at a slower speed. The following changes are seen: (1) the onset of the anacrotic limb occurs later as the pulse is transmitted peripherally; (2) starting somewhere in the axillary artery, the systolic pressure becomes progressively higher; (3) the anacrotic gradient change gradually disappears along its transmission in the axillary artery, until the anacrotic limb rises smoothly and more steeply to the systolic peak; (4) beyond the first recorded position in the aortic arch, all systolic peaks occur at the same time in relationship to the peak of the R wave of the electrocardiogram (preceding the centrally recorded systolic peak); (5) the incisura, prominent centrally, is gradually lost and is replaced by a diastolic dip ending in the dicrotic notch and followed by a dicrotic wave. Both the dicrotic notch and wave become most pronounced peripherally. In the one case of coarctation of the aorta (fig. 7*D*, *E* and *F*) the fundamental central form of the pulse is essentially unaltered in its transmission peripherally down the blood vessels of the upper limb.

In considering the transformation of the pulse it would seem that the observation of Hamilton and Dow[24] about the existence of a standing wave in the aorticofemoral system of

TABLE 2.—*Velocity of Pulse Wave Transmission in a Normal Patient (Case 3), One with Coarctation of the Aorta (Case 5) and One with Aortic Regurgitation (Case 7).*

Case	Measured Distance	Over-all Pulse Velocity	Pulse Velocity of Central Portion*	Pulse Velocity of Peripheral Portion*	Comparison of Planimetry Area of 3 Pulses†
	cm.	*M./sec.*	*M./sec.*	*M./sec.*	
3	44	8.9	7.3	11.0	Unchanged
5	42	7.5	5.6	11.5	Unchanged
7	45	11.2	9.6	16.0	Markedly changed

* Central portion is taken from aortic arch to axillary artery, peripheral portion from axillary artery to brachial artery just above antecubital fossa.

† Planimetry area refers to area under pulse curves obtained from (a) aortic arch, (b) axillary artery and (c) brachial artery. The change in area in case 7 is attributed to progressive damping of the curve as the lumen of catheter narrowed by clot.

and L. H. Peterson: Direct Measurement of Pulse Wave Velocity in Man. Am. J. Physiol. **163:** 749, 1950) describing a technic of arterial catheterization with small plastic catheters to measure directly in man the pulse velocity from the aorta to the brachial and femoral arteries.

* Since simultaneous pressure recordings could not be done, planimetric analysis of the pulse curve of beats with comparable cycle lengths was used to evaluate any change in mean pressure. Since, in conformance to Bernoulli's theorem, it has been shown that the central pulse in its transmission to the periphery neither gains nor loses significant amounts of energy, the mean pressure should remain essentially unchanged.

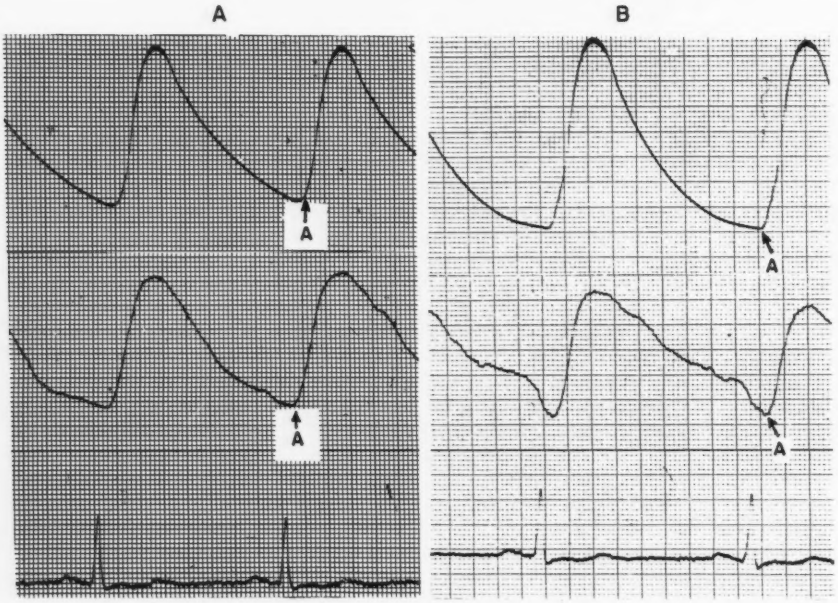

FIG. 8A. Simultaneous recordings of central aortic pressure pulse (upper), densogram of aorta (middle) and lead II of electrocardiogram (lower). Recorded at double paper speed. *B*. Simultaneous recordings of central aortic pressure pulse (upper), border tracings of the aorta (middle) and lead II of the electrocardiogram (lower). Segments *A* and *B* are both from case 7. Recorded at double paper speed. Discussed in text.

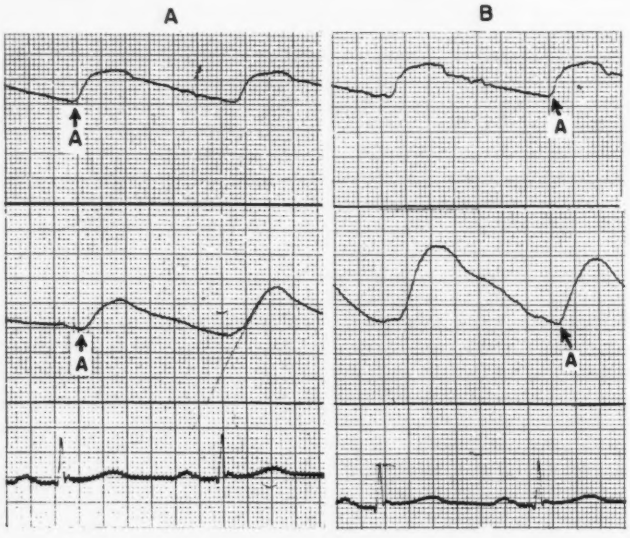

FIG. 9A. Simultaneous curves of central aortic pressure pulse (upper), densogram of aorta (middle) and lead II of electrocardiogram (lower). *B*. Simultaneous curves of central aortic pressure (upper) border tracing of the aorta (middle) and lead II of electrocardiogram (lower). Both tracings are from case 3. Recorded at double paper speed. Discussed in text.

the dog also applies essentially to the aortico-brachial system of man, with its node somewhere in the axillary artery. No effort has been made to utilize the subtraction curve to evaluate the distortion factor in addition to the standing wave, as recently described by Alexander.[25]

D. *Correlation of Central Arterial Pulse Pressure with Simultaneously Recorded Electrokymogram*

A previous report from this department[4] has dealt with the comparison of right ventricular, auricular and pulmonary artery pressures with the electrokymogram. In the present study of four cases we have attempted to define the significance of the electrokymogram of the aorta and left ventricle by means of the intraluminal aortic pressure curves in man. Electrokymographic tracings were obtained from the descending portion of the arch of the aorta and compared with the aortic pressure curve with reference to the rise of the anacrotic limb and the incisura, as a measure of the ejection phase of the left ventricle.

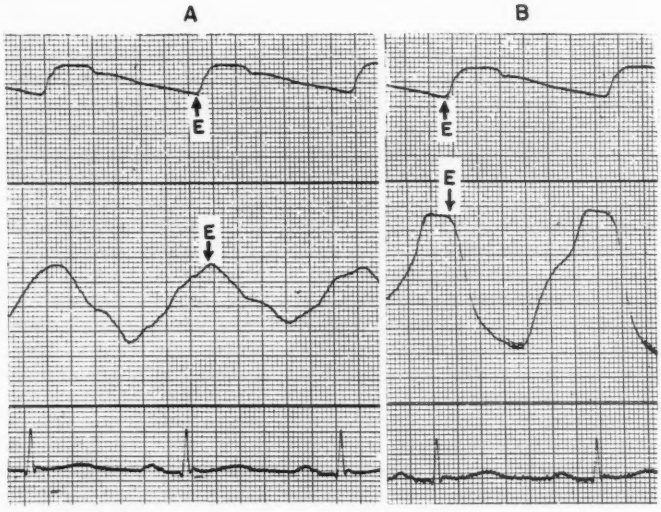

FIG. 10. Simultaneous recording of central aortic pressure pulse (upper), electrokymogram of middle of left ventricle (middle) and lead II of the electrocardiogram (lower). In *A*, middle tracing is recorded 4 cm. lower on left ventricle than in *B*. In each, *E* marks the onset of ejection. Both recordings are at double paper speed. See text for discussion.

1. Timing. In three of four cases the onset of the anacrotic limb of the aortic densogram precedes the corresponding point on the aortic pressure curve by an average of 0.03 second, range 0.01 to 0.05 second. In the fourth case, the onset of the rise of the aortic densogram follows that of the pressure curve by 0.02 second (fig. 9*A*, points A).

In all four cases the onset of the anacrotic limb of the aortic border tracing follows the corresponding point on the aortic pressure curve by an average of 0.03 second, range 0.02 to 0.04 second, with a variation between beats of 0.02 second (figs. 8*B* and 9*B*, points A).

Accurate determination of the ejection phase is impossible because none of the aortic border electrokymograms or aortic densograms has a constant or measurable incisura or notch.

2. Contour. In three of the four cases the contour of the densograms over the aortic area is surprisingly similar to the pressure pulse of this vessel (figs. 8*A* and 9*A*); of course differences between the two curves exist. The descending limb of the electrokymogram follows that of the pressure curve somewhat more faithfully than does the ascending limb.

Figures 8*B* and 9*B*, recorded from the same

patients, are border tracings from corresponding locations. The dissimilarity between the descending limb of the aortic border electrokymograms and that of the aortic pressure pulse is apparent. The anacrotic limb of the pressure pulse, however, is more faithfully reproduced in the electrokymogram.

Figure 10*A* and *B* are electrokymographic recordings from the lower and middle portions of the left ventricular border approximately 4 cm. apart, correlated with aortic pressure curves and lead II of the electrocardiogram. The striking resemblance of the ventricular electrokymogram to the ventricular volume curve of the dog is again noted. However, the marked variations between the curves only 4 cm. apart on the left ventricle border is evident.

The onset of ejection in the left ventricular electrokymograms recorded in figure 10*A* is approximately 0.05 second later than in figure 10*B* when compared with the beginning of the rise of the anacrotic limb of the aortic pressure pulse. Other phases defy accurate measurement because of indefinable endpoints. Rapid changes of gradient which occur on the pressure pulse have no constant relationship to similar changes on border electrokymograms of the left ventricle. It is thus demonstrated again[3] that the electrokymogram of the left ventricle represents an unpredictable and often distorted picture of volume changes within this chamber.

The densograms from the aorta in three of four cases follows strikingly the contour of the central arterial pulse during varying dynamic states. Border electrokymograms from similar areas of the aorta are considerably less faithful in this regard.

From this analysis and that previously reported[4] it would appear that with further refinement of the electrokymographic apparatus with respect to standardization and frequency response the densograms of the aorta and pulmonary artery may prove a valuable adjunct in the diagnosis of cardiovascular disorders as reflected in these vessels.

Summary

1. Retrograde catheterization of the aorta via the brachial artery affords a feasible method of studying directly the magnitude and contour of the arterial pressure pulse in man.

2. That this may contribute significantly to a keener insight into human cardiodynamics in health and disease was first suggested from the voluminous data comparably collected in the animal.

3. The procedure, performed by a well trained team, is no more hazardous than right heart catheterization. Complications such as cardiac arrhythmias and pain were not encountered in any of the seven cases in the present series. With careful arterial suturing and adequate sterile precautions little difficulty in preserving the radial pulse is encountered.

4. The contour of the aortic pressure pulse in normal man and in patients with hypertension, aortic regurgitation and coarctation of the aorta resemble closely comparable tracings reported in the dog. The genesis of the central pulse contour in aortic regurgitation is reconsidered.

5. The effects of cycle length, initial volume and peripheral resistance in man, especially in the presence of ventricular premature systoles and of the Valsalva maneuver, are discussed on the basis of recorded central pressure pulses.

6. The determination of the location, size, and dynamic significance of coarctation of the aorta with this technic is advocated.

7. The pulse wave transmission velocity is measured in various parts of the aorticobrachial system and the transformation of the central pulse contour along this path is described and compared with data established from animal experiments.

8. Aortic pressure pulses are compared with simultaneously recorded volume changes by means of aortic densograms and border electrokymograms from the aortic arch and left ventricle border. The advantages and limitations of the electrokymograms in the determination of the onset of ejection and in reflecting volume changes are discussed.

Acknowledgment

We are indebted to the physicians of Michael Reese Hospital for permission to study their patients and to the catheterization team for their invaluable assistance.

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Quinidine Lactate and Gluconate in the Suppression of Ectopic Ventricular Tachycardias Associated with Myocardial Infarction

Control of Toxicity by Morphine

By A. Sidney Harris, Ph.D., Antonio Estandía, M.D., Tedroe J. Ford, Jr., A.B., and Rex T. Tillotson, B.S.

In dogs with myocardial infarction, produced by a standard technic, rapid persistent ectopic ventricular tachycardia develops. Intravenous quinidine lactate and quinidine gluconate effectively control the arrhythmia in 56 to 60 per cent of the animals, but produce toxic reactions in many of them. Morphine sulfate prevents vomiting and diarrhea from quinidine, but does not prevent convulsive movements. The most effective treatment of the arrhythmia was by use of morphine followed by quinidine gluconate. This combination was successful in 89 to 100 per cent of the cases. Principles for guidance in the treatment of severe ventricular arrhythmias have been drawn from these studies.

QUINIDINE has long been known to be effective in terminating ventricular tachycardias.[1–6] In some cases, however, it has failed,[5, 6] and ventricular tachycardias have been produced by its administration.[1, 3, 7] Fatal ventricular fibrillation has occurred during slow intravenous administration of quinidine to a patient with ventricular tachycardia which developed following myocardial infarction.[8] Ventricular premature beats, brief paroxysms of ventricular tachycardia and transient ventricular fibrillation have been precipitated by quinidine in patients who were subject to spontaneous episodes of this kind.[9] Toxic manifestations of other kinds, especially nausea and vomiting, are of frequent occurrence upon intravenous administration of quinidine even when it succeeds in the abolition of abnormal cardiac rhythms.[2, 4]

Quinidine is widely regarded as the drug of choice for the treatment of ventricular tachycardias in spite of the untoward occurrences.[2, 5] It is apparent, therefore, that there is need for carefully controlled experiments to determine and analyze the conditions under which success, failure, and exacerbation of the arrhythmia result from its use. In the past, controlled study of the effectiveness of drugs and procedures in the suppression of dangerous cardiac arrhythmias of kinds similar to those which occur in patients (except arrhythmias induced by drugs) has been severely limited by the lack of a method by which such arrhythmias could be produced in experimental animals.

A technic for the production in dogs of a high frequency ectopic ventricular tachycardia associated with myocardial infarction has recently been developed.[10] Ninety per cent or more of the animals prepared by the standardized technic develop ectopic ventricular tachycardias with rates of 160 per minute or higher and rates of 200 to 260 were developed in 53 per cent of a recently tabulated series of 32 consecutive dogs. In an occasional dog the maximal ectopic rate reaches 300. The delayed ventricular tachycardia has its onset four and one-half to eight hours after occlusion of the artery, that is, after a period of occlusion that approximates the minimal duration of ischemia that is required to produce microscopically visible evidence of necrosis.[10–12] After the onset of the

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tachycardia the rate increases rapidly to a maximum which is reached within 10 to 20 hours after occlusion. The tachycardia, if untreated, typically lasts two to four days, and there may be some ectopic beats on the fifth day.

The availability of dogs with rapid ectopic ventricular tachycardia associated with myocardial infarction has provided an opportunity for controlled evaluations of the effects of drugs upon this serious arrhythmia. Using these animals after the development of a rapid and persistent tachycardia, the effects of quinidine lactate and quinidine gluconate have been studied to determine their effectiveness in the suppression of ventricular ectopic rhythms, and their toxicity. The effects of morphine in conjunction with quinidine have been studied also, and this developed into an important part of the investigation.

Materials and Technics

Fifty dogs were used in the study of ectopic impulse suppressor effects of quinidine lactate and gluconate. In addition four dogs were used in preliminary experiments in which quinidine sulfate was administered.

For surgery, the dogs were anesthetized with pentobarbital sodium, 30 mg. per Kg. Using artificial respiration and aseptic surgical technics, the anterior descending artery was ligated via a small incision in the left fourth intercostal space. The artery was dissected free at a level between 0 and 5 mm. distal to the free edge of the left auricular appendage. A doubled ligature was passed beneath the artery and cut to provide two ligatures. One of the ligatures was then tied snugly but not tightly around the artery together with a 20 gage hypodermic needle. The needle was withdrawn, leaving the artery constricted but passing some blood. The second ligature was tightened 30 minutes later, occluding the artery. The chest was closed in layers, the lungs inflated and natural respiration restored.

Electrocardiographic observations and records were made at frequent intervals. Ventricular ectopic rates and total heart rates were measured from electrocardiograms and plotted on charts.

Drug tests were begun during the morning of the first postoperative day, that is, 15 to 20 hours after occlusion. In almost all animals the ectopic ventricular rate at that time was between 180 and 250 beats per minute. In a number of animals additional tests were performed on the second and third postoperative days when the frequency of the returned or persisting ectopic ventricular tachycardia usually was lower than that which existed prior to treatment on the first postoperative day.

All drug tests were performed without anesthesia except in those trials in which morphine was used as sedation for blood pressure measurements, and to test the combined effects of morphine and quinidine upon the ectopic ventricular tachycardia, and upon the toxic manifestations.

The quinidine preparations were administered intravenously. To facilitate the injections and to insure complete control over them, a small plastic catheter was inserted into the femoral vein and kept there throughout the one, two, or more days of testing in a majority of experiments. A flexible wire was kept in the lumen of the catheter except during injections.

Dosage and Rate of Administration. A dose of 10 mg. per Kg. of the quinidine compound under test was adopted as a standard and used in all experiments except three of the early ones. The duration of an injection (governing rate of administration) was standardized at five minutes. The dose was diluted with saline to 20 cc.

Multiple control records were made at 15 to 30 minute intervals during a period of one to two hours just prior to the administration of the first dose of quinidine in each test. The term "test" is used to designate all of the repeated doses, procedures, and observations made upon an animal in any day of testing.

Results

*Quinidine Lactate.** Thirty-nine tests of the effects of quinidine lactate alone were made upon 26 dogs while fully unanesthetized and exhibiting a persistent ectopic ventricular tachycardia.

The results were strikingly variable. In 16 tests, or 41 per cent of the total number, the arbitrarily established criterion of "therapeutic success" was attained. The criterion required that the ectopic rate be reduced to zero and maintained during a period of four hours or longer at a frequency lower than one-half of that which existed during the control period just prior to the beginning of treatment. These 16 tests with most favorable results were performed upon 14, or 54 per cent, of the dogs.

Toxic signs, i.e., vomiting, diarrhea, or convulsive movements, occurred during eight of these 16 tests in which the ventricular tachycardia was most successfully controlled. In a

* The quinidine lactate and quinidine gluconate used in these studies were generously supplied by Eli Lilly and Company.

number of other tests adequate administration of the drug was interfered with by severe toxic reactions. In later experiments it was learned that the vomiting and diarrhea produced by quinidine could be totally eliminated by morphine (see sections on toxicity and on quinidine compounds after morphine). In view of these findings, the percentage of favorable results in this first series should be regarded as conservative.

Graphic and detailed representations of the results of administration of quinidine compounds are contained in the charts. Figure 1 shows the usual effects upon ectopic activity of the initial doses of quinidine lactate injected at 30 minute intervals. This was found to be the optimally effective spacing of doses for cumulative suppressor effect upon the ectopic rhythms. In this animal with an ectopic rate (total heart rate) of 230 per minute, each dose resulted in a quick but moderate diminution of the ectopic rate, and the effects were cumulative with succeeding doses. The administration was interrupted because of the advent of convulsive movements before ectopic complexes were eliminated, but the ectopic rate remained within a safely low range. The animal survived and, except for a period of convulsive movements, appeared to be in good condition at all times.

An experiment showing unusually effective suppressor action is represented in figure 2. The first dose, 10 mg. per Kg., restored an entirely normal rhythm for a few minutes, and the rate of ectopic discharging was kept at a level below one-half the control rate for an hour, though ectopic complexes were returning rapidly at the end of the hour. The addition of a second dose eliminated all ectopic activity for about two and one-half hours, after which there was a rapid increase. Following the third dose few ectopic beats were recorded during the remaining four hours of observations on that day. On the following day some ectopic activity (40 to 90 per minute) was present. A single dose sufficed practically to eliminate it. In general the higher ectopic rates (200 and above) were more difficult to control than the lower ones. Ventricular tachycardias with rates of 220 or above were distinctly more resistant to treatment than those with rates below 180. However, there were marked variations in response which could not be accounted for on a basis of ectopic rate.

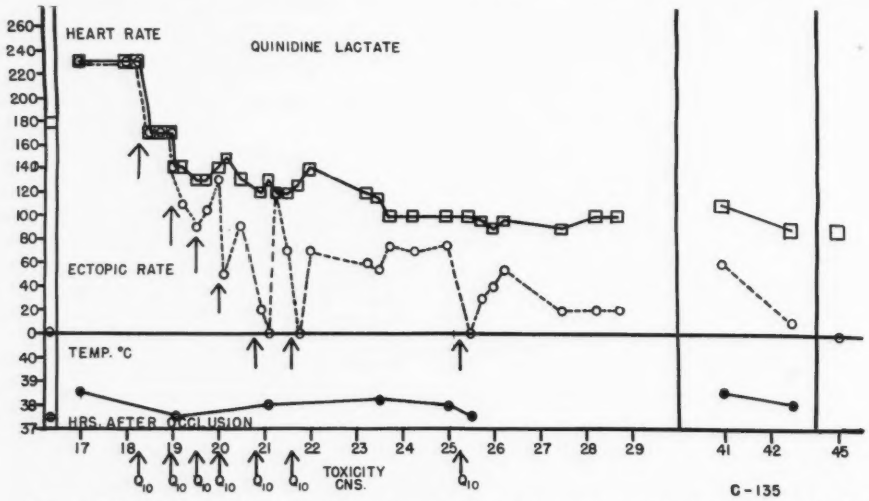

FIG. 1. Effects of quinidine lactate in animal with rapid ectopic ventricular tachycardia. Scale at left, beats per minute. Squares and solid lines, total heart rate. Circles and dash lines, ectopic rate. Each arrow indicates the time of injection of quinidine lactate, 10 mg. per Kg.

Quinidine Gluconate. The effects of quinidine gluconate alone upon ectopic ventricular tachy-

cardias were recorded during 12 tests in 10 dogs. In six, or 50 per cent, of the tests, the ectopic frequency was reduced to zero and

ments interfered more seriously in the experiments with quinidine lactate. It is probable that no significant difference in ectopic impulse

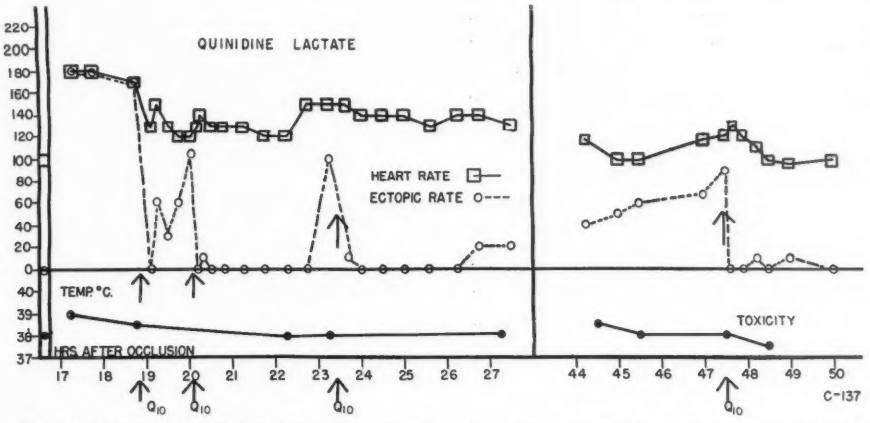

FIG. 2. Effects of quinidine lactate in animal with moderately rapid ectopic ventricular tachycardia. Keys to chart same as for figure 1.

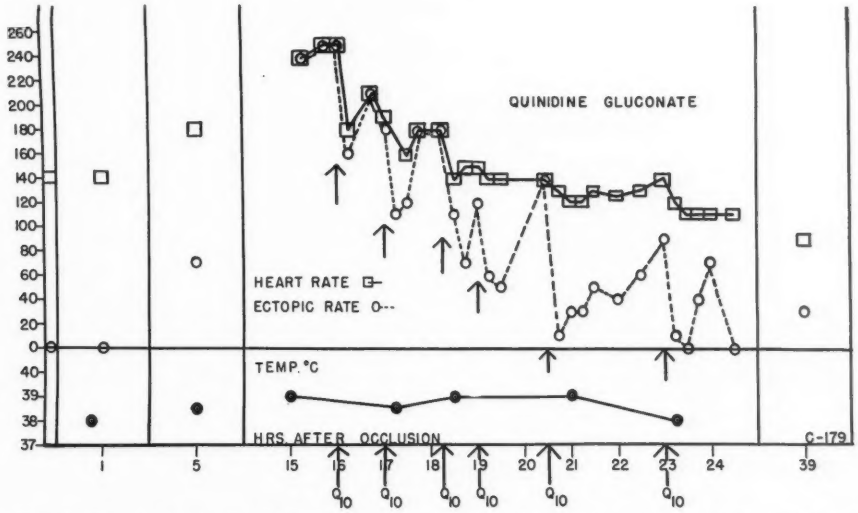

FIG. 3. Effects of quinidine gluconate in animal with rapid ectopic ventricular tachycardia. Keys to chart same as for figure 1.

maintained at less than one-half of the pretreatment rate for more than four hours. These most favorable therapeutic results were found in six dogs or 60 per cent of the total number of animals. These percentages are slightly higher than the corresponding ones obtained with quinidine lactate, but convulsive movesuppressor action is to be found between the two quinidine compounds.

A chart of one of the experiments with quinidine gluconate is reproduced in figure 3. This animal had a ventricular tachycardia with a rate of 240 to 250 on the morning of the first postoperative day prior to the first injection

of quinidine gluconate. Each dose lowered the ectopic rate immediately, and following each reduction there was a prompt rise toward the preceding high level. However, cumulative action was shown in the fact that after each additional dose the ectopic rate reached a new low level, and following the fifth dose the rise was much slower than the rises following earlier doses. After the sixth dose there was yet another rise and spontaneous fall after which no further doses were needed. Thirteen hours after the last dose the ectopic rate was only 30 per minute. This experiment is an example of successful control of a severe ventricular tachycardia by a sufficient number of doses more widely spaced than the 30 minute intervals which were found to be optimal for relatively quick suppressor effects.

Quinidine Lactate following Morphine in Strongly Analgesic Doses. Six tests of the ectopic suppressor effects of quinidine lactate following morphine were carried out in five dogs. In four of the six tests ectopic activity was abolished for a time and maintained at a frequency less than one-half of the control rate for more than four hours. The two failures were first and second postoperative day tests in the same resistant animal. Effective suppression of ectopic impulses was achieved in four of five animals, but one of them died in standstill one hour after the last dose. In three of the tests, all in the successfully controlled group, there was a significant diminution in ectopic frequency, though not a large one, between the injection of morphine and the first dose of quinidine lactate.

Quinidine Gluconate following Morphine. Nine tests of the effects of quinidine gluconate following morphine upon ectopic ventricular tachycardia were performed in nine dogs. All ectopic activity was eliminated temporarily in each of the animals and the ectopic rate was below one-half of the control rate longer than four hours (six hours to permanent) in eight of them and possibly the other one also. Unfortunately records from one animal were discontinued two and one-half hours after ectopic activity was brought under control. At least 89 per cent, and possibly 100 per cent, of the morphine-quinidine gluconate animals belong in the well-controlled group. Between the administration of morphine and the first dose of quinidine gluconate the ectopic frequency declined significantly in six of the nine dogs. This observation together with a similar one in the morphine-quinidine lactate experiments may indicate that morphine alone has a minor ectopic impulse suppressor effect, but it appears more probable that the inconstant reductions in frequency resulted from general sedation.

Toxic Reactions. Vomiting, diarrhea, and convulsive movements figured prominently in the results of both quinidine compounds, gluconate and lactate. Since the experiments were performed for the study of the suppressor effects of these drugs upon ectopic impulses, the number of 10 mg. per Kg. doses administered was determined by the persistence, disappearance, and recurrence of ectopic activity, except that in some experiments the administration of quinidine had to be interrupted or postponed because of the severe toxic reactions.

In the 39 tests with quinidine lactate alone vomiting occurred in 10, or 26 per cent, and convulsive movements in nine, or 23 per cent. Diarrhea accompanied the vomiting in a few experiments, and in one test defecation without vomiting occurred after each dose. Quinidine gluconate alone produced vomiting in three of 13 tests, or 23 per cent, and convulsive movements in one, or 8 per cent. The incidence of vomiting was about equal with the two quinidine compounds, but convulsions occurred in a significantly higher percentage of cases and were more prolonged in the experiments with quinidine lactate.

In the 15 tests in which morphine was given one to three and one-half hours prior to the first dose of quinidine (six with lactate, nine with gluconate), no vomiting or diarrhea occurred. Convulsions occurred in three. Morphine was administered subcutaneously in all trials. The doses in milligrams per kilogram were 5 in nine trials, 4.5 in two trials, 2 in two trials, 7 in one trial, and 7.5 in one trial.

The administration of morphine to a dog commonly induces vomiting. When repeated doses of morphine were injected, however, only the first one induced vomiting. Morphine gave complete protection against the induction of

vomiting by additional morphine (see Leake[13]) just as it protected against the induction of vomiting and diarrhea by quinidine.

Blood Pressure. Systolic, diastolic, and mean blood pressures were recorded from the femoral artery in a number of experiments via a small plastic catheter connected with a Statham gage transducer modified for use with a carrier-frequency amplifier.* A Sanborn Poly-Viso Cardiette recorded the pressure tracing and electrocardiogram simultaneously (fig. 4). The recording was changed from mean to systolic-diastolic pressures for a few beats in a majority of trials, thus permitting mean pressure and pulse pressures to be measured. This change could be made instantaneously by turning a valve.

Mean pressure measurements just before and immediately after injections of quinidine lactate, 10 mg. per Kg., injected slowly during a period of five minutes, revealed that the pressure dropped during 17 injections and remained unchanged in one. The range of the diminutions was 0 to 45 mm. Hg. The average decline was 18 mm. Hg. Recovery of the mean pressure was 50 to 80 per cent complete in 15 minutes and 75 to 100 per cent complete in 30 minutes. The one injection that produced a 45 mm. drop was given to an animal that died shortly afterward.

Upon administration of quinidine gluconate in the same dosage by the same technic, the mean blood pressure fell during 15 injections, rose during two (both in the same animal) and was unchanged in one. The range of modification was +40 to −45 mm. Hg. The average change was a drop of 16 mm. Hg, which is almost identical with the average result obtained with quinidine lactate. The rate of recovery from the diminutions in pressure following injections of the two quinidine compounds were equal also.

Charts showing the mean blood pressure reactions together with the ectopic impulse suppressor effects of quinidine gluconate are reproduced in figures 5 and 6. The blood pressure reactions of these two animals were very different. Each animal had received morphine, 5 mg. per Kg., for analgesia more than three hours before the first dose of quinidine. The experiment illustrated in figure 5 was unique in that

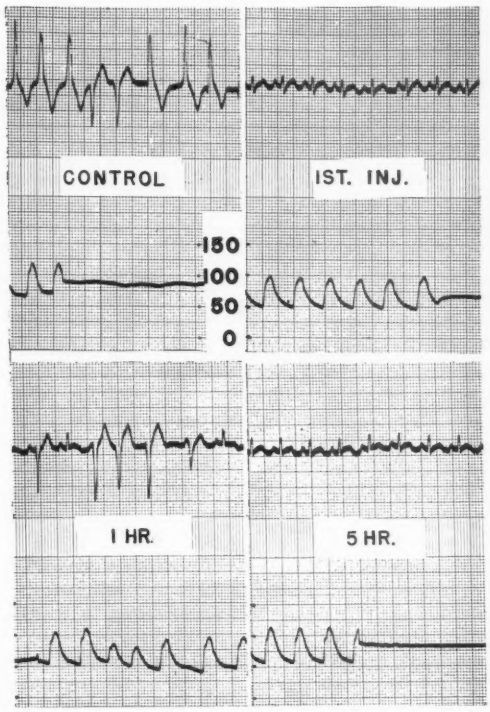

FIG. 4. Electrocardiograms and systolic-diastolic and mean arterial pressure records in dog with ectopic ventricular tachycardia while under test with morphine and quinidine gluconate. *Control*, one and one-half hours after morphine sulfate, 5 mg. per Kg., but before first dose of quinidine gluconate. Prior to morphine, ectopic rate was 230. At time of control, ectopic rate averaged 180 in a longer record. *1st inj.*, immediately after first dose of quinidine gluconate, normal rhythm and somewhat reduced blood pressure. *1 hr.*, record made 1 hour after first dose of quinidine gluconate and 30 minutes after second dose, showing recurrence of ectopic rhythm and status of the arterial pressures. *5 hr.*, record made 5 hours after first dose of quinidine gluconate and 1 hour after the fifth and last dose, showing a lasting normal rhythm and normal arterial pressures (115/60).

the only rises in mean pressure during quinidine injections that were recorded during the whole series of experiments occurred in this animal.

The fact that the rises in pressure occurred only after the third dose and during the fourth

* Made by Southwestern Industrial Electronics Co., Houston, Texas.

and fifth may perhaps be correlated with the observation that convulsions usually occurred after three or more doses if they occurred at all. Convulsions are indicative of central nervous system excitation, and the increases in blood pressure could have resulted from nervous excitation on a subconvulsive level. Impulses could radiate from cranial nuclei to the heart and vasoconstrictor effectors via sympathetic pathways. The increase in heart rate following the third, fifth, and seventh doses may tend to confirm this interpretation though the rises in pressure and in rate could logically be explained as results of vagal paresis.[14, 15] Other suggestions (a) that the rises in blood pressure might have resulted from increased cardiac output due to improvement in pumping, and (b) that they might have resulted from an increased blood volume due to additions of saline were judged to be improbable or relatively unimportant factors. Otherwise, rises in pressure should have occurred in all animals, not in one alone.

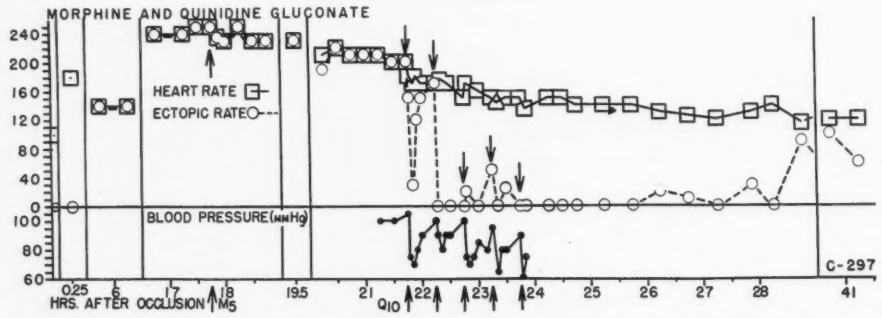

FIG. 5. Effects of morphine and quinidine gluconate upon rapid ectopic ventricular tachycardia and mean blood pressure.

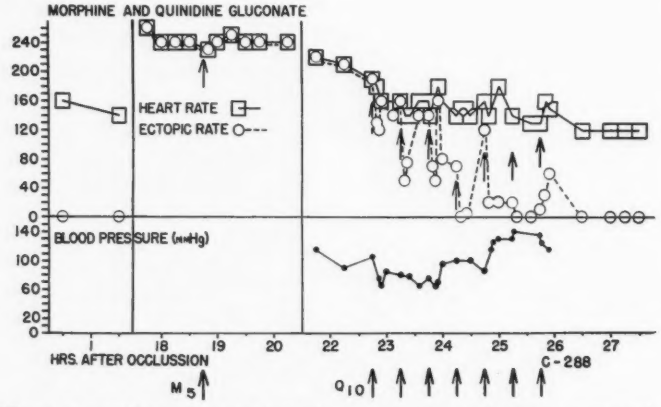

FIG. 6. Effects of morphine and quinidine gluconate upon rapid ectopic ventricular tachycardia and blood pressure in an unusual animal in which some of the quinidine injections produced rises in the mean blood pressure.

The diminutions in pressure could, conceivably, be due to more than one effect of quinidine also. There is evidence that it produces vasodilation[16–18] and weakens the contraction of cardiac muscle,[17] although in some experiments small doses have increased the shortening of auricular and ventricular muscle[18, 19] with no change in rate, or even an increase. In one study in which increased excursion of the ven-

tricular myograph was reported, an increase in the dose of quinidine resulted in weakening of the ventricular muscle.[19]

Pulse pressures were significantly reduced during the dip in mean pressures in a number of trials in our series. This suggests that the systolic discharge was reduced, but does not prove it because the femoral pulse pressure is greatly influenced by superimposed waves which are subject to reduction by a lowering of the peripheral resistance. Experiments with skeletal muscle and perfused hearts, summarized by Sollmann,[20] support the view that quinidine weakens contraction.

Vasodilatation appears to be a very sensitive reaction to quinidine, and it is probable that this is the chief cause of the decline in mean blood pressure that follows the injection of a small or moderate dose. Following a very large dose or a succession of doses within a brief period, weakening of the myocardium and vasodilatation both probably contribute to the production of hypotension.

Production or Exacerbation of Ectopic Ventricular Tachycardia by Quinidine. This response was observed in three experiments. In two of them paroxysms of ventricular tachycardia accompanied convulsive movements.

The association of the production of ventricular ectopic activity with the occurrence of convulsions in some cases following the administration of quinidine may be regarded as circumstantial evidence that these increases in ectopic activity may have been induced by increased nervous activity. It is well known that sympathetic nerve excitation and injected epinephrine can produce or facilitate the production of ectopic ventricular beats.[21–23]

Although recent studies have shown that sympathetic impulses to the heart constitute only a relatively minor factor in the production of the ectopic ventricular tachycardia which develops with myocardial infarction in the dog,[24] a large increase in the discharge of cardiac sympathetic impulses and of epinephrine, induced by quinidine excitation of the nervous system, could be the excitatory mechanism which produces the ectopic activity in these exceptional cases. This concept places the ectopic impulse production by quinidine upon the same basis as the blood pressure raising effect. Both are relatively infrequent reactions to the administration of quinidine.

Fatalities: Danger Signs. A total of six deaths occurred during or soon after testing procedures. Three animals died during tests with quinidine lactate alone, two died during tests with quinidine lactate and morphine, and one died during the night following a test in which quinidine gluconate and morphine were used. Certain observations from the records of these animals may contribute to better recognition and evaluation of signs of danger during treatment with quinidine, especially via the *intravenous* route.

Since widening of the QRS deflection has long been recognized as a sign of quinidine action and since lengthening beyond certain limits has become a sign of overdosage, the durations of QRS at various stages of these six experiments with fatalities have been measured carefully.

Four of the six animals that expired exhibited widening of the QRS deflection by 75 to 100 per cent or more before death, but one of these four developed the widening and died after only one dose (10 mg. per Kg.) of quinidine. This animal and two others that did not develop significant widening of QRS constitute 50 per cent of the fatality cases. In one-half of these cases, therefore, no warning could have been obtained from the duration of the QRS deflection prior to the final dose. Furthermore, a number of animals among the 44 survivors developed prolongation of QRS by as much as 100 per cent. Such a prolongation cannot be regarded as a sure sign that death is imminent. Nevertheless, a great prolongation should be heeded as a warning. The practice of withholding quinidine after the QRS is prolonged by 50 per cent[2] appears to be conservative and desirable. Since significant prolongation does not occur in all quinidine fatalities, other signs are needed.

Two of the six animals that died during testing exhibited intense dyspnea. One of them had only a moderate dyspnea before the first dose of quinidine, but the degree of dyspnea became more severe after each dose. This animal died five minutes after the injection of the

third dose. The other fatality case with intense dyspnea exhibited the dyspnea prior to the administration of quinidine and died after only one dose, 10 mg. per Kg. In certain other animals, some increase in respiratory movements followed the administration of quinidine, but these increases were moderate and lasted for only a few minutes, coinciding with the brief period of reduced blood pressure that was commonly observed. Dyspnea was produced by quinidine in only the one animal cited.

Dyspnea was rare in the 50 dogs with myocardial infarction used in this study. In addition to the two fatality cases, this sign was noted in the protocol of only one other dog, and that observation was on the third postocclusion day when the dog had a normal heart rhythm with a rate of 90. The dog had received no treatment since the first postocclusion day when a rapid ventricular tachycardia was brought under control by three doses of quinidine gluconate.

Blood pressure was recorded continuously during the quinidine tests in 11 of the 50 animals. Two of the fatalities were from these 11 cases. The mean pressures prior to the first quinidine injections were distributed as follows: two dogs, 105 mm. Hg; one dog, 100 mm.; two dogs, 90 mm.; two dogs, 85 mm.; four dogs, 70 mm. Both of the dogs that died were from the 70 mm. group.

With so few cases of marked dyspnea and hypotension as a basis, perhaps no conclusions should be reached, but the observations upon these fatalities suggest that in the presence of either of these conditions quinidine and other depressant drugs should be used only with great care.

Discussion

Comparison of Results Obtained in Dogs with Data in Clinical Reports. The ventricular tachycardias which are being studied in the dog preparations begin after a period of four and one-half to eight hours following occlusion. The severity of the ventricular tachycardia increases rapidly during the next few hours as the infarction develops.

Numerous authors have reported clinical ventricular tachycardias that were associated with myocardial infarction. The collection of human cases that can be correlated most definitely with the observations on dogs are those of Armbrust and Levine.[5] In their series of 107 patients with paroxysmal ventricular tachycardia, 79 cases, or 74 per cent of the series, had coronary disease as the underlying cause of the tachycardia. In 44 cases, the attack was associated with acute myocardial infarction. The onset of the ventricular tachycardia occurred *most often on the first day of the infarction*, though the incidence was high on each day of the first two weeks. The finding of most frequent onset on the first day conforms to the observations in the dog with a large infarct.[10] The onset of tachycardia in some patients after a delay of a number of days differs from the dog with its maximal delay of eight hours. It is possible, however, that in some patients the initial symptoms resulted from obstruction of a relatively small artery which did not produce ectopic activity, and that the ventricular tachycardia was produced some days later as a result of additional occlusions or extension of the thrombosis with enlargement of the necrotizing mass of muscle. The differences in time of onset of the tachycardia with respect to time of occlusion may be apparent differences only.

In the cases of Armbrust and Levine the attacks of tachycardia were of two kinds, intermittent and persistent. The intermittent attacks were short paroxysms, lasting seconds or minutes, which ceased spontaneously or were readily controlled by therapy. The persistent type of attack was more difficult to control. In 31 persistent episodes of ventricular tachycardia, intravenous quinidine was successful in controlling the attacks in 20 cases or 65 per cent of them. This percentage of favorable results in patients with severe arrhythmias lies within the range of percentages of successful results in the dogs with the persistent high frequency tachycardias.

In the dog experiments also there were a few animals with intermittent ventricular ectopic rhythms which ceased spontaneously or were easily suppressed by drugs, and a larger number of animals with persistent high frequency tachycardias which required larger amounts of quinidine for control, and some of these severe

arrhythmias could not be controlled by quinidine.

Recent studies upon blood quinidine concentrations in patients have shown that in order to raise the blood level to the 4 to 9 mg. per liter range found necessary to restore sinus rhythm, the required dosage was 0.4 to 0.6 Gm. of quinidine every two hours for five doses.[6] The highest concentration was required in a case of paroxysmal ventricular tachycardia. A dose of 0.6 Gm. to a 70 Kg. man would be 8.6 mg. per Kg., closely approaching the 10 mg. per Kg. doses used in the dog experiments. Five doses also approximate the average number of doses required during the several hours of a test in severe ventricular tachycardia in the dog. It should be remembered that our studies with dogs have been concerned with only the ectopic ventricular tachycardias that arise in association with acute myocardial infarction. No comparisons with arrhythmias arising from other causes are as yet attempted.

Nature of the Arrhythmia and Mechanism of Its Suppression. Critical examination of the electrocardiograms (see fig. 4) reveals evidence that the abnormal complexes must be due to discrete ectopic ventricular impulses, and not to re-entrant conduction. Re-entrant conduction would be continuous conduction within intraventricular circuits. Intraventricular conduction is represented in the electrocardiogram by the QRS deflection. Therefore re-entrant conduction in the ventricles, if it existed, would produce continuous QRS complexes, that is, each QRS would be joined to the next one before and after. This is clearly not to be found in a great majority of records. In the ventricular tachycardia record reproduced in the control electrocardiogram of figure 4 the QRS deflections are widely separated from each other, occupying no more than about one-fifth of the total time in the record instead of the entire time as continuous intraventricular conduction would require. As the frequency of abnormal complexes is reduced by treatment, the separations become wider. In extremely fast ventricular tachycardias, 300 per minute and above, the wide QRS deflections that commonly are found in such frequencies often appear to be joined or nearly so. Under these conditions there is grave danger of a change from ventricular tachycardia to ventricular fibrillation, a condition that *is* characterized by continuous conduction.[25] In view of the universally branching syncytium that makes up the musculature of the ventricles, it is highly improbable that re-entrant conduction could occur in a cyclic manner in the ventricles for more than one or two beats before conduction would become disorganized into fibrillation. It is concluded that the ventricular tachycardia results from ectopic impulses arising in ventricular muscle. In previous papers evidence that these impulses arise in the boundary of the infarct has been presented[26,27] and the probable excitatory factors discussed.[10] The reduction of the ventricular tachycardia by quinidine therefore is attributed to its suppressor action upon ectopic pacemakers in agreement with Gold.[2]

Clinical Implications. The similarities in the reactions of dogs with persistent high frequency ventricular tachycardias accompanying myocardial infarction to the reported reactions of patients with similar tachycardias, following intravenously administered quinidine compounds, suggest that observations made upon this kind of animal preparation may be of value in deriving principles for the improvement of treatment of this kind of severe ventricular arrhythmia.

The main conclusions of a practical nature which can be drawn from the present series of experiments are the following: (a) In order to eliminate a high frequency ectopic ventricular tachycardia, or to produce a lasting reduction of the ectopic frequency to a safe level, it *usually* is necessary to administer large and relatively frequent doses of quinidine (as compared with the usual regime) during the first few hours. (b) A large dose of morphine sulfate, administered subcutaneously, has been found effective in stopping or preventing all vomiting and diarrhea which might result from quinidine administration. (c) In *exceptional cases* one or two standard doses of quinidine (10 mg. per Kg., slowly infused) are sufficient to control the arrhythmia. Administration should be stopped when this point is reached. (d) In *other exceptional cases* even one or two standard doses can be fatally toxic. In this series, the

animals that died after only a small amount of quinidine exhibited intense dyspnea, hypotension, or prolongation of the normally initiated QRS complex by as much as 75 to 100 per cent of the control. These are regarded as important warning signs that quinidine should be withheld or that caution must be used in administering any further doses. The four fatal cases reported by Armbrust and Levine[5] were described as having pulmonary edema, congestive heart failure, and shock. (e) It is not necessary to eliminate all ventricular ectopic beats, and in some cases it is dangerous to attempt to do so. A reduction of the rate of an ectopic ventricular tachycardia from 200 to 250 per minute to 100 will abolish danger of ventricular fibrillation[27] and may be calculated to improve pumping action enough to markedly reduce the danger of cardiac and circulatory failure.[2] (f) During the treatment of a persistent high frequency ventricular tachycardia with quinidine, and other ectopic suppressor drugs as well, *the constant presence and frequent use of an electrocardiograph should be required.* This is necessary in order to make use of the principles summarized in c, d, and e.

Summary

A method of producing animal preparations with rapid, persistent, ectopic ventricular tachycardia associated with myocardial infarction has been developed. These animals duplicate some of the major features exhibited by patients with myocardial infarction in whom a severe ventricular arrhythmia arises, including types of arrhythmia and reactions to quinidine.

Four series of experiments were performed with these animal preparations. The tests made in the four groups were as follows: (1) tests with quinidine lactate alone, (2) tests with quinidine gluconate alone, (3) tests with morphine sulfate followed by quinidine lactate, and (4) tests with morphine sulfate followed by quinidine gluconate.

In series 1, 2, and 3 the percentages of animals in which successful control of the arrhythmia was achieved in one or more tests were 54, 60, and 60, respectively. No significant difference appears in these results. In series 4, in which morphine sulfate was followed by quinidine gluconate successful control was achieved in 89 to 100 per cent of the animals. These results are regarded as therapeutically superior to those of the other three groups.

Vomiting, diarrhea, and convulsions complicated a number of the experiments. The incidence of vomiting was about equal following quinidine gluconate and lactate. The incidence of convulsions was greater following quinidine lactate.

Morphine sulfate, 5 mg. per Kg., stopped or completely prevented vomiting and diarrhea from both quinidine preparations. Morphine did not stop or prevent convulsions.

During injections the blood pressure declined somewhat in almost all cases. In one animal the pressure rose following some injections.

Paroxysms of ectopic ventricular tachycardia were induced by quinidine injections in three of the 50 animals. Convulsive movements accompanied the paroxysms in two animals. The unusual paroxysms are attributed to increased excitation of the central nervous system and consequent sympathoadrenal stimulation of the heart.

Study of the six fatalities indicates that quinidine administration may be especially dangerous in the presence of marked dyspnea or pronounced hypotension. Prolongation of QRS is not present to serve as a warning sign in all cases, but when it does exist in marked degree, administration of quinidine should be stopped.

Evidence is presented to show that the abnormal rhythm is due to ectopic impulses and not to re-entrant conduction. The reduction in abnormal activity by quinidine is due to suppression of ectopic pacemakers.

From the observations a list of principles which should be of value in the treatment of severe ventricular tachycardias has been formulated.

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Studies of the Antiadrenergic Effects of Nitroglycerin on the Dog Heart

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Using anesthetized dogs, the possible antiadrenergic effects of nitroglycerin upon the myocardium were studied. Observations were made upon changes in heart rate, myocardial oxygen consumption, systolic vigor, and the electrocardiograms. Data are presented showing the effects of nitroglycerin and adrenergic agents when given separately and in combination. Results indicate that in dogs, nitroglycerin produces no antiadrenergic effects on the myocardium. The suggestion is made that the T wave changes seen after adrenergic stimulation in dogs may not be due to anoxia.

THE beneficial effects of nitroglycerin in the anginal syndrome have been considered to be due either to coronary dilation with an improvement in myocardial oxygenation, or to the reduction in peripheral resistance and cardiac work, or to both, resulting in a decrease in myocardial oxygen requirement. However, in view of recent evidence of heart rate and electrocardiographic changes in atropinized cats, Raab[1-3] suggests that nitroglycerin acts in a different manner. He postulates that it interferes with the metabolic, anoxia producing effects of the sympathomimetic amines on the myocardium. Although this hypothesis is attractive, Raab admits that its proof depends upon further evidence.

The question then arises as to the criteria required for more conclusive study of this problem. Large increases in myocardial oxygen consumption in dogs occur after cardiac accelerator nerve stimulation with little or no increases in heart rate.[4-8] The records of Raab[2] show rather small rate increases after stimulation of the stellate ganglion or after the infusion of epinephrine. Therefore, it would seem that changes in heart rate do not critically demonstrate adrenergic anoxating effects. Whether the depression of the T wave in the electrocardiogram which is seen after adrenergic stimulation is due to anoxia or to some other myocardial effect of adrenergic agents is more difficult to establish. (See Discussion.)

There are, however, two changes induced by adrenergic agents which occur together, and which can serve as indicators for testing any deviation in the adrenergic effects upon the myocardium. These are (1) changes in vigor of contraction, as indicated in the aortic pressure pulse, and (2) changes in myocardial oxygen consumption.[4-8] The present report deals with our attempts to modify these adrenergically induced myocardial changes in dogs by the use of nitroglycerin.

Methods

Dogs were anesthetized with pentobarbital, and under artificial respiration the left chest was opened between the third and fourth ribs. The blood was made noncoagulable with 100 to 150 mg. of heparin. The left jugular vein was cannulated to administer fluid and to return coronary sinus blood. The coronary sinus was cannulated via the right auricle, and the cannula was made secure in the sinus by the inflation of a small balloon at the cannula tip.

The left common coronary artery was dissected free and was cannulated by means of the special cannula previously described.[9] The cannula was connected to the constant pressure apparatus and a Shipley rotameter described elsewhere.[8, 10] In a few cases adjustment of the position of the cannula was necessary to get adequate sealing without leakage or restriction of coronary inflow. The possibility of leakage was tested in two ways: (1) With perfusion pressure above aortic pressure, a ligature was tightened about the common left artery distal to the cannula. The rotameter was then observed for evidence of flow and therefore of leakage. (2) After clamping the inflow rotameter tube, a side arm on

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the outflow side of the rotameter was opened. Leakage was present when a steady flow occurred from the open side arm. When this occurred slight repositioning of the cannula stopped the leakage and produced a to and fro motion of blood at the open side arm. After the proper placing of the cannula, leakage never developed during the course of the experiment.

In a few instances the septal artery was occluded by the cannula. In each such case the origin of this artery was very far central. Its occlusion was always suspected because of rapid decreases in blood pressure with abnormal rhythms or pulsus alternans.

In most of the experiments a portion of the coronary sinus blood was led through the cuvette of a Waters-Conley oximeter to indicate directional sinus oxygen changes and proper timing for blood samples. In some cases electrocardiograms were taken. Usually lead II was used.

In all experiments the following data were obtained: aortic pressure, perfusion pressure, total left coronary flow, arterial and coronary sinus oxygen levels by the method of Van Slyke and Niell,[11] and oxygen consumption per 100 Gm. of perfused myocardium. After the control studies were made, the observations were repeated following the use of nitroglycerin, Parke - Davis Adrenalin, *l* - epinephrine,* *l*-Arterenol* and stimulation of the cardiac accelerator nerves as described below. The rotameter was calibrated with the animals' own blood. At the end of each experiment dilute India ink was injected into the coronary cannula and the injected area was cut out and weighed.

Results

1. *Effects of Nitroglycerin Alone.* After controls were obtained, nitroglycerin was injected into the coronary cannula with a motor-driven syringe. The results in table 1*A* show that nitroglycerin produced elevations in coronary flow and coronary sinus oxygen content with no appreciable change in myocardial oxygen consumption or heart rate. The doses of nitroglycerin were purposely small in order to produce coronary dilation without marked changes in blood pressure.

2. *Effects of Nitroglycerin during Cardiac Accelerator Nerve Stimulation.* Control data were obtained. The left cardiac accelerator nerve was stimulated after section from the stellate ganglion. New observations were made and immediately nitroglycerin was injected into the coronary cannula. Further observations were made. The results (table 1*B*) show that nerve stimulation, as is usual, resulted in increased coronary flow and oxygen consumption with a decreased coronary sinus oxygen content. The injection of nitroglycerin produced further increases in coronary flow with an elevation of sinus oxygen content in all but one experiment (D6). There was no significant change in oxygen consumption or consistent alteration of heart rate except in D1. Our records (not shown) gave no evidence that nitroglycerin altered the form of the aortic pressure pulse. Larger doses of nitroglycerin produced the typical fall in blood pressure but did not influence the vigor of contraction.

3. *Effects of Nitroglycerin on the Action of Commercial Adrenalin.* These experiments were done in two ways. (A) After the controls were obtained Adrenalin was injected into the perfusion chamber or into the coronary cannula. As soon as blood samples were drawn, nitroglycerin was injected. Blood samples were again drawn. (B) In these experiments blood samples and records were obtained in the following order: (1) control, (2) after injection of Adrenalin, (3) control, (4) after injection of Adrenalin plus nitroglycerin. Table 1*C* shows the results. Again it is striking that nitroglycerin in doses sufficient to dilate the coronary arteries produces no consistent change in oxygen consumption. In experiments D4, D9 and D10 significant cardiac slowing occurred. However, since these dogs were not atropinized and blood pressure tended to rise, reflex slowing is likely.

4. *Effects of Nitroglycerin on the Action of l-Epinephrine and l-Arterenol.* These experiments were done as in 3 above. *l*-Epinephrine was given in doses of 1 gamma and nitroglycerin in a dose of 0.84 mg. The dose of *l*-Arterenol was 0.5 gamma. The results of these experiments (table 1*D*) indicate that nitroglycerin did not modify the heart rate or the oxygen consumption. The electrocardiogram revealed the usual T-wave inversion after these adrenergic drugs. Intracoronary injection of even this huge dose of nitroglycerin did not modify this T-wave response. Figure 1 shows a typical record. *A* and *B* show the effects

* The *l*-epinephrine and *l*-Arterenol were supplied by the Sterling Winthrop Research Institute, Rensselaer, New York.

TABLE 1

Exp	Procedure	M.B.P. mm. Hg	Heart Rate	Coronary Sinus O_2 Volumes %	A-V O_2 Diff.	Left Coronary Flow cc./100/Gm./1 min.	O_2 Consumption cc./100/Gm./1 min.	Remarks
	A. Effects of Nitroglycerin on Control Heart							
D3	Control	102	190	5.5	13.5	69	9.36	
	After Nitroglycerin	91	189	8.9	10.3	88	9.43	65 γ in 60 sec. Intracoronary
D4	Control	61	200	4.2	7.9	116	9.16	
	After Nitroglycerin	60	200	5.0	6.8	142	9.65	65 γ in 30 sec. Intracoronary
D6	Control	58	190	3.5	11.2	47	5.28	
	After Nitroglycerin	60	195	4.3	10.5	53.5	5.62	65 γ in 30 sec. Intracoronary
	B. Effects of Nitroglycerin during Sympathetic Nerve Stimulation							
D1	Control	80	200	5.9	9.5	116	11.0	
	During Nerve Stim.	92	200	4.2	13.7	155	21.3	
	With Nitroglycerin	88	195	8.2	6.5	228	14.9	13 γ in 2 sec. Intracoronary
D2	Control	75	130		10.2	29	2.9	
	During Nerve Stim.	67	200		12.0	109	13.1	
	With Nitroglycerin	72	180		10.2	128	13.0	200 γ in 100 sec. Intracoronary
D3	Control	82	185	5.2	13.2	57	7.5	
	During Nerve Stim.	102	190	3.5	14.8	73	10.8	
	With Nitroglycerin	85	190	7.0	10.9	94	10.3	200 γ in 100 sec. Intracoronary
D5	Control	43	170	5.5	9.3	66	6.1	
	During Nerve Stim.	56	186	1.9	12.8	136	17.5	
	With Nitroglycerin	55	161	3.5	10.9	157	17.2	250 γ in 50 sec. Intracoronary
D6	Control	35	180	3.3	11.2	40	4.4	
	During Nerve Stim.	59	188	1.5	12.0	147	17.7	
	With Nitroglycerin	48	184	1.3	12.7	127	16.1	260 γ in 1 min. Intracoronary
D7	No Control	91	190			80		
	During Nerve Stim.	100	190	3.9	14.0	112	15.7	
	With Nitroglycerin	106	180	6.0	11.7	138	16.2	220 γ in 50 sec. Intracoronary
	No Control	60	165			92		
D10	During Nerve Stim.	62	161	1.9	9.4	117	11.0	
	With Nitroglycerin	52	160	3.5	7.7	143	11.0	260 γ in 1 min. Intracoronary
	C. Effects of Nitroglycerin on the Action of Commercial Adrenalin							
D4	Control	64	190	5.0	5.0	159	7.9	
	After Commercial Adrenalin	84	178	4.7	5.0	220	10.0	200 γ into Perfusion Chamber
	With Nitroglycerin	109	82	5.3	3.9	275	10.0	300 γ in 70 sec. Intracoronary
D9	Control	59	190			72		
	After Commercial Adrenalin	86	135	1.3	13.1	152	19.4	50 γ in Perfusion Chamber
	With Nitroglycerin	68	100	5.4	9.6	162	15.5	260 γ in 1 min. Intracoronary
D10	Control	72	170		8.2	95	7.9	
	After Commercial Adrenalin	80	138	4.2	9.0	132	11.7	50 γ in Perfusion Chamber
	With Nitroglycerin	79	151	3.0	7.8	165	12.9	260 γ in 1 min. Intracoronary

TABLE 1—*Continued*

Exp.	Procedure	M.B.P. mm. Hg	Heart Rate	Coronary Sinus O_2 Volumes %	A-V O_2 Diff.	Left Coronary Flow cc./100/Gm./1 min.	O_2 Consumption cc./100/Gm./1 min.	Remarks
	C. Effects of Nitrogen on the Action of Commercial Adrenalin—Continued							
D13	Control	84	180	6.4	9.5	100	9.5	
	After Commercial Adrenalin	77	167	5.9	9.3	133	12.9	5 γ in 2 sec. Intracoronary
	Control	77	165	6.9	8.3	92	8.3	
	After Commercial Adrenalin and Nitroglycerin	84	167	6.2	8.8	122	11.2	5 γ Adrenalin, 65 γ Nitroglycerin in 2 sec.
	D. Effects of Nitroglycerin on the Action of l-*Epinephrine and* l-*Arterenol (Intracoronary Injections)*							
D21	Control	87	145	2.0	9.4	50	4.7	
	Intracoronary in 2 Sec. 1 γ *l*-Epinephrine	72	144	1.7	9.4	132	12.4	T Wave Inversion
	Control	66	135	3.2	9.1	42	3.8	
	Intracoronary in 2 Sec. 1 γ *l*-Epinephrine, 0.84 mg. of nitroglycerin	40	158	1.9	10.6	142	15.0	T Wave Inversion
D22	Control	81	170	4.5	11.0	67	7.3	
	Intracoronary in 2 Sec. 0.5 γ *l*-arterenol	76	154	2.7	12.4	121	15.0	T Wave Inversion
	Control	95	160	3.6	11.5	71	8.1	
	Intracoronary in 2 Sec. .5 γ *l*-arterenol, 0.84 mg. nitroglycerin	76	161	4.7	10.5	139	14.6	T Wave Inversion
	E. Effects of Nitroglycerin on the Action of l-Arterenol (Intravenous Injection)							
	Control	75	160	8.0	9.5	65	6.1	
	Jugular Infusion in 5 Sec. 10 γ *l*-arterenol.	144	140	4.0	14.4	114	16.4	T Wave Inversion
	Control	88	160	8.9	8.9	69	6.1	
	Jugular Infusion in 5 Sec. 10 γ arterenol, 3.36 mg. nitroglycerin	107	180	4.3	13.8	132	18.2	T Wave Inversion

of *l*-Arterenol on the aortic pressure pulse, total left coronary flow and continuous oximeter cuvette tracings of changes in coronary sinus oxygen level. The record shows the usual changes induced by adrenergic agents; namely, the shortening of systole, the temporary increase in blood pressure and the increase in coronary flow. Since the oximeter does not receive capillary blood immediately, there is a lag in its response, the length of which depends upon the speed of blood flow. *B* shows that in spite of the increase in blood flow the oximeter response shows a decreasing coronary sinus oxygen content.

In contrast to records *A* and *B*, records *C*, *D* and *E* show the effects of a mixture of *l*-Arterenol and nitroglycerin. The coronary flow curve shows striking differences in that it increases much earlier and its rate of increase is more rapid. The oximeter curve in D shows at first a rise in sinus oxygen content due to the coronary dilation induced by nitroglycerin. Nevertheless, in E the oximeter curve shows that the effect of the adrenergic agent is to decrease the sinus oxygen content in spite of a marked fall in blood pressure.

5. *Effects of the Intravenous Injections of Nitroglycerin and* l-*Arterenol.* For these experi-

ments, after control observations were made *l*-Arterenol (10 gamma) was injected intravenously and data obtained. Again controls were established and were followed by the intravenous injection of a mixture of 10 gamma of *l*-Arterenol and 1.84 mg. of nitroglycerin. Table 1*E* shows the results when both the rate after nitroglycerin. The points above and below *C* show effects of adrenergic agents on oxygen consumption and heart rate respectively. The points above and below *D* indicate similarly the changes after both adrenergic agents and nitroglycerin. Line *E* indicates the average percentage change in oxygen consump-

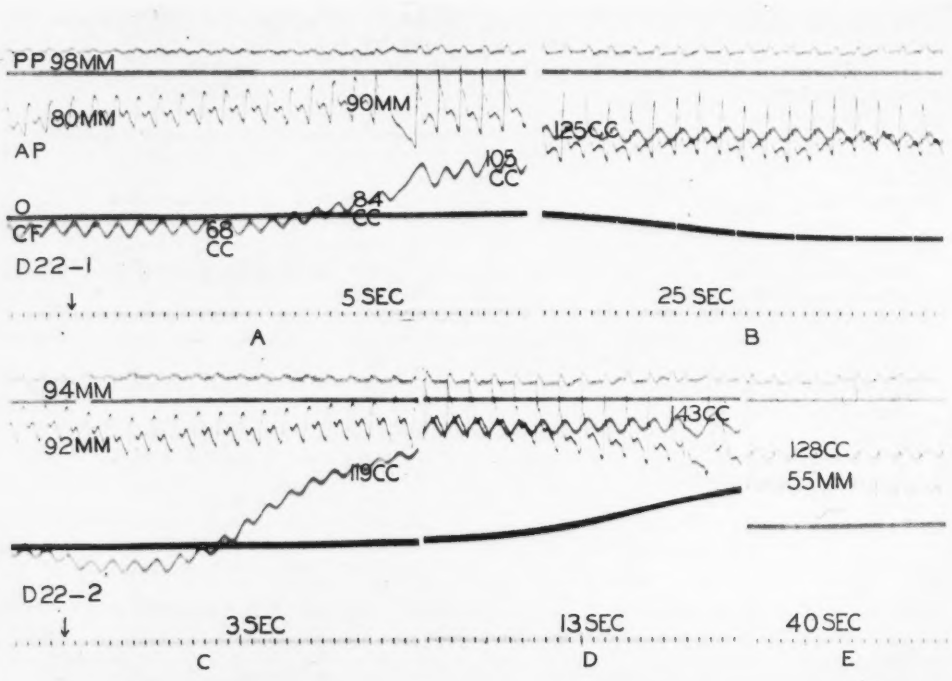

FIG. 1. Actual record showing effects of intracoronary injection of *l*-Arterenol in *A* and *B* and mixture of 0.5 gamma of *l*-Arterenol and 0.84 mg. of nitroglycerin in *C*, *D* and *E*. P.P., perfusion pressure; A.P., aortic pressure; C.F., coronary flow; O, oximeter cuvette tracing. Upward deflection indicates rising coronary sinus oxygen content. Arrows indicate point of injection. Time in 1/5 and 1/50 second.

peripheral and cardiac effects of these drugs are in operation. Here again nitroglycerin does not modify the changes either in oxygen consumption or in the electrocardiogram which are induced by *l*-Arterenol.

Figure 2 is a composite of all the experiments and shows the changes (expressed in per cent of the control values) in heart rate and oxygen consumption. The effects of nitroglycerin alone on oxygen consumption are shown by the points at *A*. The points at *B* show the heart tion. No average line has been drawn for changes in heart rate. This composite indicates (1) that the intracoronary injection of physiologically active amounts of nitroglycerin does not modify oxygen consumption or heart rate, (2) that nitroglycerin does not alter the adrenergically induced elevation in oxygen consumption, and (3) that the increase in myocardial oxygen consumption produced by adrenergic agents may occur without increases in heart rate.

Since our results were at variance with those of Raab it was thought that the use of atropine might have produced the differences. Therefore, atropine, 1 mg. per Kg., was given to dogs. Even in these animals nitroglycerin did not modify the changes in pulse rate or in the T wave induced by adrenergic agents.

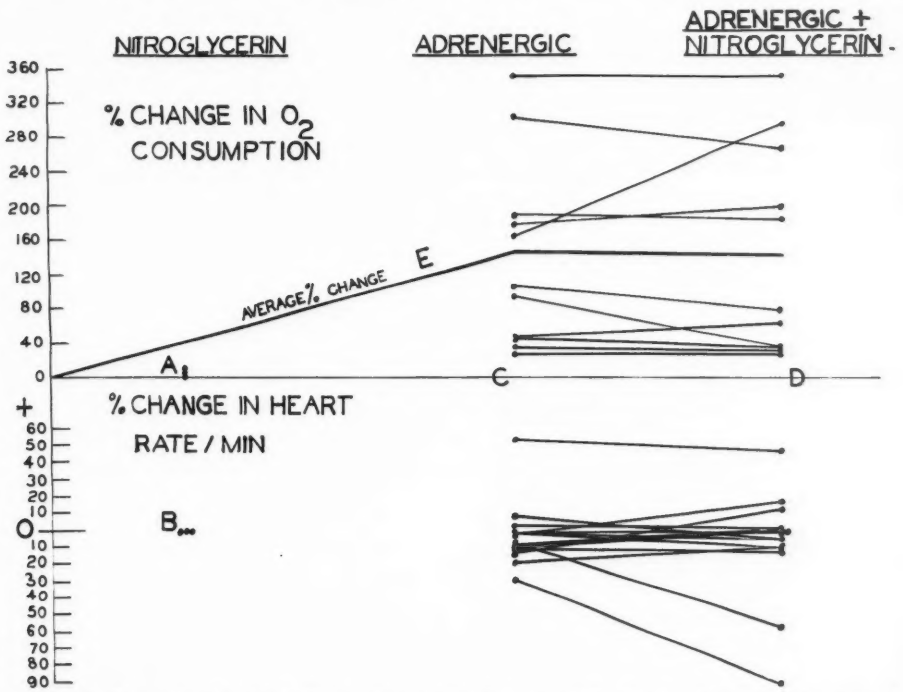

FIG. 2. Composite graph of all experiments showing percentile changes from control values of oxygen consumption and heart rate. *A*, oxygen consumption, and *B*, heart rates, after nitroglycerin alone. Points above and below *C* show changes in oxygen consumption and heart rate respectively after adrenergic agents. Points above and below *D* show data after nitroglycerin and adrenergic agents. *E* shows average percentile change in oxygen consumption.

COMMENT

The use of the new coronary cannula in these and other experiments has been highly satisfactory. With this instrument, cannulation of the left common coronary has become a simple procedure. The usual patterns of coronary behavior in magnitude, time or direction of response have not been modified. With previous cannulas, the use of a tight ligature certainly damaged the arterial walls and probably blocked the intra-arterial nerves. The constancy of results by all methods lends support to the view that the peripheral coronary responses are not altered either by damage to the central vessels or even by their actual section. Since other nerves exist, these observations do not necessarily prove the absence of coronary reflexes.

It is clear from the experiments on dogs that nitroglycerin even in large doses does not modify the changes in myocardial oxygen consumption, in systolic vigor, in heart rate, or in the electrocardiogram which are induced by adrenergic stimulation.

These results do not support the theses of Raab, namely that nitroglycerin metabolically reduces the anoxating properties of adrenergic agents. The evidence presented by Raab, however, is indirect since it is not based on actual measurements of changes in myocardial oxygen consumption, but rather on heart rate and electrocardiographic changes. It is noteworthy,

too, that our results in dogs even fail to support his electrocardiographic and heart rate findings.

These differences raise the questions (1) as to whether cats and dogs differ in their response to nitroglycerin and the adrenergic agents, and (2) as to whether the observed T-wave inversions are due to anoxia. A comparison of our records with those of Raab do reveal a rather striking difference in that in our dogs the T wave inverted very promptly while in his records the T-wave inversion occurred much later. However, the answer to the second question is of far more importance. We seriously doubt that the T-wave pattern produced by adrenergic agents in our experiments is due to myocardial anoxia. There are several reasons for such a view. In our experiments it was extremely difficult to produce such T-wave changes even by prolonged clamping of the common left coronary. They occurred only after profound myocardial anoxia resulting in decreases in blood pressure. Adrenergic stimulation even in the presence of myocardial anoxia always produced the usual deep T-wave inversion. Therefore, we suggest that adrenergic agents must in some way alter the direction of repolarization which may bear no relationship to their anoxating properties. In our opinion conclusions as to the degree of myocardial oxygenation which are based on simple T-wave inversion in the presence of adrenergic stimulation are open to criticism. Finally, it should be stated that this work does not alter the views that nitroglycerin may improve myocardial oxygenation by coronary dilation and/or that it may reduce the myocardial oxygen requirement by a reduction in peripheral resistance.

Summary

The effects of nitroglycerin upon heart rate, myocardial oxygen consumption and electrocardiograms were studied, both before and after adrenergic stimulation. The results indicate that in dogs, nitroglycerin, even in large doses, produces no metabolic effect upon the myocardium which can be considered as antiadrenergic. The suggestion is made that the T-wave changes seen after adrenergic stimulation in dogs may not be due to anoxia.

Acknowledgments

We wish to thank Mr. Morton Eleff and Miss Martha McClaren for their technical assistance in these experiments.

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Effect of Pulse Pressure and Mean Arterial Pressure Modification on Renal Hemodynamics and Electrolyte and Water Excretion

By EWALD E. SELKURT, PH.D.

Studies were conducted to evaluate the influence of pulsatile versus nonpulsatile arterial perfusion pressure on plasma flow, filtration rate, sodium excretion, and urine volume. Through a wide range of mean renal arterial pressures, reduction of pulse pressure was without effect on renal function. The level of the mean arterial pressure, however, had a very dominant role in the electrolyte and water handling, decreases and increases in excretion paralleling the direction of change of the mean pressure. These alterations were observed even though filtration rate and plasma flow exhibited a marked degree of autonomy in the face of these pressure variations. Mechanisms by which these modifications in salt and water excretion could result from alteration in the mean arterial pressure are discussed.

THE diminution of urinary sodium excretion with reduction in filtration rate in acute experiments in dogs has been verified by several groups of investigators.[1–4] In the initial investigation,[1] it was disclosed that as arterial perfusion pressure was reduced from an average of 148 to 123 mm. Hg, glomerular filtration rate and blood flow at first were decreased to only a minor extent, if at all, due presumably to mechanisms which favored autonomy of the renal circulation. Yet with reduction in filtration rate of only 7 per cent, sodium excretion decreased to about one-half of the control average. More recently, Blake and co-workers[3] and Mueller and associates[4] have detected significant decreases in sodium excretion following compression of the renal artery even when no changes in filtration rate as measured by present technics were observable. The question was therefore raised as to whether sodium excretion is regulated by filtration rate to the precise degree inferred by the above investigations, or whether other hemodynamic variables inevitably altered by the experimental procedures, such as reduction of pulse pressure and mean arterial pressure, could in some other manner influence sodium and water excretion.

Hooker[5] believed that reduction of pulse pressure during the course of perfusion of isolated kidneys was able to reduce blood flow and urine volume. Gesell,[6] conducting studies in the intact canine kidney, apparently refuted the claim that change in pulse pressure might alter blood flow, but nevertheless believed that reduction in pulse pressure caused diminution in urine flow and in chloride excretion. Considering another aspect of the problem, although disagreement exists concerning the exact influence of arterial pressure on renal interstitial pressure,[7–8] it is conceivable that changes in renal interstitial pressure could modify processes of diffusion proceeding in the kidney. Thus at least two tentative variables resulting from arterial pressure modification are worthy of consideration in relation to the modifications of renal function suggested above.

The problem of modification of the pulse pressure and the mean arterial pressure and its influence on renal function was approached in three ways in the present investigation. In the first group of experiments the effect of altering pulse pressure at constant mean arterial pressure on glomerular filtration rate, renal plasma flow, sodium excretion, and urine vol-

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ume was examined. In the second group, mean arterial pressure was first decreased with subsequent alteration of pulse pressure. In the third group, with the view that effects initiated by procedures in the second group should be reversed by increasing mean pressure, arterial pressure was elevated with subsequent alteration of the pulse pressure at the higher levels.

Methods

Mongrel dogs (12 male, four female) averaging 20.5 Kg. in weight (14.5 to 29.5) supplied the pertinent data of this investigation. Either

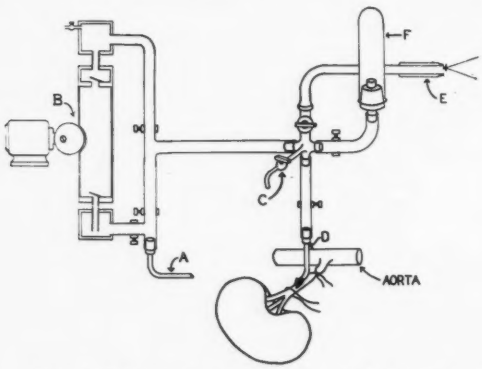

Fig. 1. Schematic presentation of the perfusion circuit for varying mean and pulse pressure to the experimental kidney. *A:* carotid artery cannula; *B:* pump (see text); *C:* outflow cannula for arterial blood sampling; *D:* renal arterial cannula; *E:* Gregg optical manometer; *F:* damping chamber (large size lusteroid test tube).

pentobarbital anesthesia (30 mg. per Kg. intravenously) or chloralose (125 mg. per Kg. intravenously) was used to prepare the animals for the necessary surgical procedures. Maintenance doses were given to preserve a uniform level of anesthesia throughout the subsequent experimental procedures. Surgery involved exposure of the left kidney by a dorsal retroperitoneal approach, catheterization of both ureters suprapubically with plastic tubing, and exposure of the carotid and femoral arteries and jugular and femoral veins. Infusion of Ringer's, Locke's, or 0.9 per cent sodium chloride solution was begun after completion of surgery and continued during the clearance experiment. Giving only average figures, a volume of 380 ml. was infused during 48 minutes prior to the beginning of the clearance observations and continued at a rate of 6.7 ml. per minute during the urine collection, so that a total of 1160 ml. of fluid was infused.

Prior to the cannulation procedures, anticoagulant was administered, either heparin (4 mg. per Kg. initially, and a total of 5 mg. every half hour), Paritol* (50 mg. per Kg. initially, and a total of 50 mg. every half hour), or combinations of both in half proportion. The renal artery was cannulated after ligation of its axis at the junction of the abdominal aorta, care being taken not to disturb the renal nerve fibers. Blood was then perfused immediately from the carotid artery via the external circuit shown in figure 1.

The circuit illustrated in the figure permitted a wide range of variation of mean arterial pressure and pulse pressure. For normal arterial pressure the kidney was perfused directly from the carotid cannula, *A*, through the direct external circuit into the renal arterial cannula, *D*. A four-way metal cannula permitted connection of this circuit to a Gregg optical manometer, *E*, of suitable sensitivity and frequency, a pulse-damping chamber, *F*, and an outflow cannula, *C*, for obtaining arterial blood samples for analysis of clearances. When reduction in arterial pressure was desired, this was achieved by partial clamping of the Tygon tubing just above the carotid cannula. When elevated perfusion pressures were desired, the pump circuit to the left was connected into the circuit. The main unit of the pump† consists of thick-walled Elastomold tubing of 3.5 cm. outside diameter and 12 cm. length. Rubber flap valves permit movement of blood in one direction only. Pumping action was obtained by a rotary ball-bearing cam, *B*, driven by a Bodine motor which turned at 120 revolutions per minute. The motor was mounted on a screw arrangement (not shown) by which adjustment of the position of the cam and hence the stroke volume could be obtained. Damping of the pulse was

* The Paritol was supplied through the kindness of Dr. Joseph Seifter of the Wyeth Institute of Applied Biochemistry, Philadelphia, Pa.

† The pump was constructed by Mr. Clifford Wilson, Lilly Research Laboratories, Indianapolis City Hospital, Indianapolis, Ind.

obtained by opening the damping chamber, *F*. All parts of the circuit were connected by Tygon tubing of 10 mm. outside diameter to minimize resistance. Lead tubing was used in the manometer circuit.

Details of the procedure for conducting the clearance studies were as follows: When the effects of damping the pulse at constant mean arterial pressures were studied, two control periods preceded the damping, two periods were collected during the damping, and finally two recovery periods concluded the experiment. In the second type of experiment, following two control periods, mean arterial pressure was reduced to about 90 mm. Hg, accompanied by some reduction in pulse pressure. Two urine collection periods followed. Then the pulse was obliterated by opening the damping chamber, after which periods 5 and 6 were collected with no further change in mean pressure. During periods 7 and 8 the pulse was restored, still with maintenance of the reduced mean pressure. Finally, both mean pressure and pulse pressure were restored during the recovery periods 9 and 10. In the third type of experiment the pump was connected into the circuit. After two control periods pressure was elevated to an average of 184 mm. Hg with concomitant increase in pulse pressure. After periods 3 and 4 the pulse pressure was reduced to about a third with continued elevation of mean pressure during periods 5 and 6. Periods 7 and 8 showed recovery as the pressures were restored to approximately control values.

A mercury pump infused creatinine and paraaminohippurate (PAH)* at a rate adequate for maintenance of blood levels at concentrations suitable for estimation of glomerular filtration rate and effective plasma flow. Ten minute collection periods were observed throughout, with appropriate discard periods. The left kidney was the experimental one, and the right served as the simultaneous control for nonspecific factors which might be operative during the course of the experiment to modify the clearances. Therefore, all definitive data are based on comparison of the experimental (L) with the control (R) as ratios. Chemical methods used were those which have been described elsewhere.[1, 9]

Results

A. Reduction of Pulse Pressure with Constant Mean Arterial Pressure. A representative experiment (No. 3 of table 1) is plotted in figure 2. Data on paraaminohippurate and creatinine clearance (UV/P),† sodium excretion, and urine volume are given in this and subsequent figures as ratios L/R from above downward. At the bottom of the figure are the

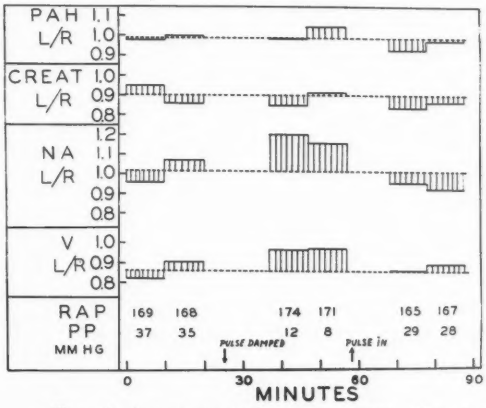

FIG. 2. A representative experiment (No. 3 of table 1) showing the influence of damping of the arterial pulse at constant mean pressure. Values are expressed as ratios of the experimental (*L*) to control (*R*) for paired simultaneous collection periods. RAP: renal arterial mean pressure; PP: pulse pressure.

mean renal arterial pressures (RAP) and pulse pressures (PP) for the experimental kidney for each stage of the experiment. In this experiment no change in paraaminohippurate and creatinine clearance (UV/P) resulted as the pulse pressure was decreased from 35 to 12 mm. Hg. Sodium excretion and urine volume increased slightly (average of 1.02 to 1.19 and 0.87 to 0.97 respectively), but this was not a systematic trend in the six experiments of table 1, for

* We are indebted to Dr. Karl H. Beyer of Sharp and Dohme, Inc., of Glenolden, Pa., for the supply of paraaminohippurate used in these experiments.

† UV/P is the renal plasma clearance, which is one minute's excretion, UV, divided by the concomitant plasma concentration, P. U and P are the urinary and plasma concentrations of the given substance, and V is the urine volume per minute.

TABLE 1.—*The Effect of Decrease in Pulse Pressure with Constant Mean Renal Arterial Pressure*

Expt.	Control* L/R	Pulse Damped* L/R	Recovery* L/R	Statistical Analysis:† Comparison of Stage 1 (pulse damped) with control	
PAH UV/P (ml./min./kidney)					
1	1.11	1.12	1.07	Mean of the differences of Control	
2	1.02	1.09	1.10		2.15
3	0.99	1.02	0.96	Mean of the differences of Experimental	
4	0.91	0.89	0.84		−1.82
5	0.91	0.86	0.90	*t*	0.662
6	0.94	0.83	0.82	*p*‡	0.50
Av.	0.98	0.96	0.94		
Creatinine UV/P (ml./min./kidney)					
1	1.07	1.14	1.09	Mean of the differences of Control	
2	0.95	0.93	1.01		3.33
3	0.90	0.88	0.87	Mean of the differences of Experimental	
4	0.84	0.82	0.79		−4.68
5	0.98	0.91	0.97	*t*	0.333
6	0.79	0.61	0.69	*p*	0.75
Av.	0.92	0.87	0.90		
Sodium Excretion (microequiv./min./kidney)					
1	1.23	0.90	0.88	Mean of the differences of Control	
2	1.28	1.00	1.24		−25.17
3	1.02	1.19	0.94	Mean of the differences of Experimental	
4	0.73	0.86	0.84		−22.33
5	0.72	0.77	0.91	*t*	.073
6	0.99	0.64	0.68	*p*	>.90
Av.	0.98	0.88	0.90		
Urine Volume (ml./min./kidney)					
1	1.21	1.00	0.90	Mean of the differences of Control	
2	1.58	0.97	1.25		−0.007
3	0.87	0.97	0.89	Mean of the differences of Experimental	
4	0.82	0.95	0.96		−0.103
5	0.83	0.88	1.00	*t*	0.575
6	1.24	0.89	1.11	*p*	0.60
Av.	1.06	0.95	1.01		
MABP Av.	168	169	162		
mm. Hg S.D.	±8	±15	±15		
P.P. Av.	43	8	34		
mm. Hg S.D.	±3.8	±3.4	±4.3		

* All values in this and subsequent tables are average of two consecutive periods. At the request of the Editor, data are given only as ratios of L (experimental) to R (control). However, if absolute data are desired, they will be supplied on request by the author. The data relevant to the statistical analysis are retained in terms of the original values of ml. per min. for paraaminohippurate (PAH) and creatinine clearance (UV/P) and urine volume, and in microequivalents per min. for sodium.

† For method of analysis, see p. 77, Snedecor, G.W.: Statistical Methods. Iowa State College Press, 1946.

‡ p is calculated for $2(n-1)$ degrees of freedom.

three showed small increases and three showed decreases. Considering the group as a whole, the differences between left and right kidney function in periods with pulse decreased were not significantly different from the control group (p = >0.90 for sodium and p = 0.60 for urine volume). This was true also for paraaminohippurate and creatinine (p = 0.50 and 0.75 respectively).

B. Reduction of Pulse Pressure following Decrease in Mean Arterial Pressure. Experiment 7 of table 2 is presented in figure 3 to illustrate the findings in this group. The paraaminohippurate clearance was not altered by reduction in mean arterial pressure from 187 to 84 mm. Hg, nor was it subsequently modified in any way by alteration of the pulse pressure at this level. Nor was filtration rate (creatinine clearance (UV/P)) altered after reduction of renal arterial pressure (RAP) and decrease in pulse pressure (periods 5 and 6). This function tended to decrease slightly in periods 7 and 8 with prolongation of the reduced arterial pressure.

Sodium excretion decreased markedly with reduction in mean perfusion pressure to 0.23 of control and remained at 0.24 with elimination of the pulse. Urine volume showed a corresponding alteration, falling to 0.33 of control in stage 1 of reduced pressure and continuing at 0.34 in stage 2. Restoration of the pulse in stage 3 had little effect on these functions. On restoration of mean arterial pressure, sodium excretion and urine volume typically did not return to control during the time of observation.

It is important to emphasize that in this experiment, as well as in number 8, marked reduction in sodium excretion and urine volume resulted with no apparent decrease in filtration rate, considered as ratios. It would appear that a dominant factor in bringing about these changes was the reduction in mean arterial pressure. In the other experiments of table 2 there was some decrease in filtraton rate so that it is possible that reduction in sodium load was a contributary factor to the decreased elimination of sodium and water.

Considering the data summarized in table 2 the following conclusions appear warranted on the basis of statistical analysis of the combined data: Decrease in mean renal arterial pressure from 149 to 88 mm. Hg has no effect on paraaminohippurate clearance, nor is this function modified in any way by subsequent alteration (decrease and restoration) of pulse pressure. Although the creatinine clearance (UV/P) decreases from an average of 0.91 to 0.85 in stage 1 of reduced pressure, the differences between the experimental and control clearances are not significantly increased (p = 0.25), nor does elimination of the pulse alter this relationship (p = >0.90).

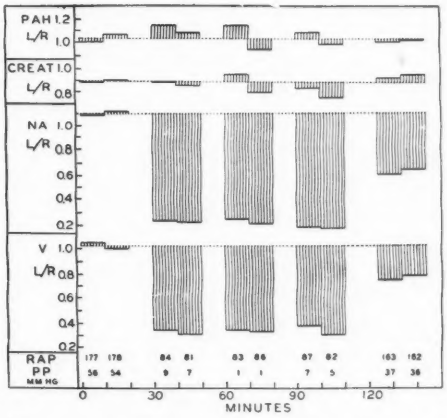

FIG. 3. Representative experiment showing the effect of decrease in pulse pressure after reduction of mean perfusion pressure (experiment 7 of table 2). After reduction of pulse pressure in stage 2 it was again restored during stage 3 even while the mean pressure remained reduced to about 85 mm. Hg.

The effects of reduction of mean arterial pressure on sodium excretion and urine volume, however, are much more marked. Thus, sodium excretion decreases from an average ratio of 0.91 to 0.36 in stage 1 (p = 0.05), and urine volume shows a proportional but slightly less decrease (0.93 to 0.44) (p = <0.05). No further change in either function results with decrease in pulse pressure.

C. Reduction in Pulse Pressure following Increase in Mean Arterial Pressure. In this group the pump was used throughout to supply the perfusion pressure for the experimental kidney. The femoral arterial pressure was used as a reference for the control kidney pressure. Initial adjustments were made so that the pump sup-

TABLE 2.—*The Effect of Alteration in Pulse Pressure Following Reduction in Mean Perfusion Pressure*

Expt.	Control	Stage 1	Stage 2	Stage 3	Recovery	Statistical Analysis:	Comparison of Stage 1 with Control	Comparison of Stage 2 with Stage 1
	L/R	L/R	L/R	L/R	L/R			
PAH UV/P (ml./min./kidney)								
7	1.03	1.12	1.06	1.04	1.02	Mean of the differences		
8	0.95	1.07	1.08	1.08	0.95	of Control	4.43	3.86
9	0.92	0.86	0.84	0.86	0.81	Mean of the differences		
10	0.88	0.83	0.81	0.82	0.85	of Experimental	3.86	5.80
11	1.00	0.99	0.92	0.91	0.89	t	0.099	0.282
						p	>.90	0.80
Av.	0.96	0.97	0.94	0.94	0.90			
Creatinine UV/P (ml./min./kidney)								
7	0.89	0.88	0.88	0.80	0.95	Mean of the differences		
8	0.98	0.97	0.94	0.95	0.91	of Control	3.82	6.20
9	0.87	0.78	0.79	0.76	0.81	Mean of the differences		
10	0.91	0.81	0.82	0.84	0.90	of Experimental	6.20	6.22
11	0.91	0.82	0.74	0.78	0.78	t	1.24	0.009
						p	0.25	>.90
Av.	0.91	0.85	0.83	0.83	0.86			
Sodium Excretion (microequiv./min./kidney)								
7	1.11	0.23	0.24	0.19	0.64	Mean of the differences		
8	0.82	0.46	0.52	0.40	0.60	of Control	50.2	240.0
9	0.94	0.41	0.35	0.29	0.47	Mean of the differences		
10	0.69	0.15	0.16	0.16	0.40	of Experimental	240.0	221.4
11	0.99	0.56	0.49	0.54	0.68	t	2.20	0.176
						p	.05	.90
Av.	0.91	0.36	0.35	0.32	0.55			
Urine Volume (ml./min./kidney)								
7	1.02	0.33	0.34	0.35	0.77	Mean of the differences		
8	0.92	0.57	0.64	0.57	0.72	of Control	0.3	1.70
9	1.02	0.42	0.39	0.35	0.51	Mean of the differences		
10	0.69	0.21	0.25	0.24	0.43	of Experimental	1.7	1.59
11	0.99	0.65	0.60	0.68	0.78	t	2.78	0.177
						p	.03	.90
Av.	0.93	0.44	0.45	0.44	0.64			
RAP Av.	149	88	90	91	156			
mm. Hg S.D.	±17	±6.3	±7.4	±8.4	±5.3			
P.P. Av.	45	12	1	11	42			
mm. Hg S.D.	±9.7	±2.6	—	±3.8	±10			

plied approximately the same mean and pulse pressure as recorded in the renal artery before connecting the pump to the circuit. This is illustrated in figure 4 in which appear a series of tracings from each stage of a representative experiment (No. 14 of table 3). It is seen that

he pump delivered a pulsatile pressure with ontour resembling the normal renal arterial ulse. Indeed, when proper adjustments of pres- ures were made prior to starting the experi-

The constancy of effective plasma flow and filtration rate in the face of increased arterial pressure is confirmed by all of the experiments of this group ($p = 0.30$ for paraaminohippurate

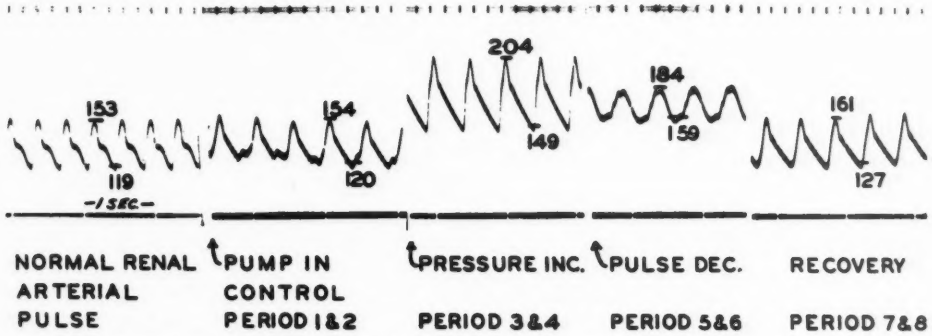

FIG. 4. Representative pulse tracings obtained in the renal arterial perfusion circuit in experiment 14 of table 3 while using the pump. To the left of the record appears the normal arterial pulse before inclusion of the pump. Systolic and diastolic pressures in mm. Hg are inscribed on the record.

ments, all clearances showed a reasonably good starting correspondence. The degree and nature of alteration of the pressure pulses during the experimental stages are exemplified by this figure.

The effects of these alterations in pressure are diagrammed in figure 5. No change in paraaminohippurate and creatinine clearance resulted when pressure was increased from 137 to 176 mm. Hg, nor did decrease in pulse pressure from 55 to 24 mm. alter these clearances. Despite no apparent increase in filtration rate, sodium excretion increased markedly from 0.89 to 1.47 of control, and urine volume from 0.92 to 1.50 during stage 1. In this experiment a further increase in these functions was noted when the pulse pressure was reduced in stage 2, but it could not be decided whether this was directly due to decrease in pulse pressure or the result of further increase in the ratio of the perfusion pressure of the experimental kidney over that of the control kidney (as measured by the femoral pressure) from 1.13 to 1.20 in stage 2. This resulted because the systemic arterial pressure manifested a gradual decline even as the experimentally elevated perfusion pressure was kept relatively constant by the use of the pump. This trend operated in most of the experiments of this group (table 3).

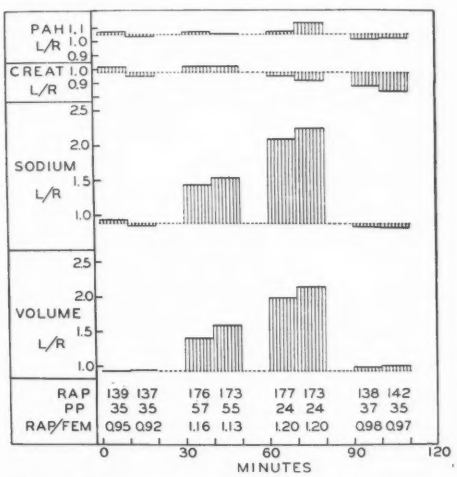

FIG. 5. Representative experiment (No. 14) showing the influence of increase in mean perfusion pressure with subsequent effect of reduction in pulse pressure in stage 2. The ratio RAP/FEM at the bottom of the figure is the ratio of the renal arterial pressure over the simultaneous femoral arterial pressure, taken to be representative of the control kidney arterial pressure.

and $p = 0.20$ for creatinine when comparing differences in stage 1 with control). Again, reduction of pulse pressure has no significant effect on these functions ($p = 0.90$ and $p = 0.60$ respectively when comparing differences

TABLE 3.—*The Effect of Increase in Mean Perfusion Pressure with Subsequent Decrease in Pulse Pressure*

Expt.	Control L/R	Stage 1 L/R	Stage 2 L/R	Recovery L/R	Statistical Analysis	Comparison of Stage 1 with Control	Comparison of Stage 2 with Stage 1
PAH UV/P (ml./min./kidney)							
12	0.88	0.95	0.98	0.92	Mean of the Differences of		
13	0.84	0.96	0.97	0.91	Control	5.4	−0.14
14	1.05	1.06	1.10	1.02	Mean of the Differences of		
15	0.96	0.93	0.96	0.91	Experimental	−0.14	−0.80
16	0.96	1.07	1.03	0.85	t	1.15	0.170
					p	.30	.90
Av.	0.94	1.01	1.01	0.92			
Creatinine UV/P (ml./min./kidney)							
12	0.78	0.84	0.92	0.84	Mean of the Differences of		
13	0.79	0.88	0.87	0.82	Control	4.3	1.50
14	0.98	1.02	0.94	0.87	Mean of the Differences of		
15	0.85	0.89	0.89	0.84	Experimental	1.5	2.37
16	0.97	1.08	0.99	0.82	t	1.34	0.56
					p	.20	.60
Av.	0.87	0.94	0.92	0.84			
Sodium Excretion (microequiv./min./kidney)							
12	0.85	1.43	1.66	1.14	Mean of the Differences of		
13	0.74	1.31	1.98	1.68	Control	37.6	−101.8
14	0.89	1.47	2.16	0.84	Mean of the Differences of		
15	0.82	1.37	1.89	1.25	Experimental	−101.8	−137.0
16	0.89	1.85	3.20	1.15	t	3.35	0.715
					p	.01	.50
Av.	0.84	1.48	2.12	1.18			
Urine Volume (ml./min./kidney)							
12	0.92	1.49	1.83	1.14	Mean of the Differences of		
13	0.88	1.35	1.91	1.40	Control	0.094	−0.84
14	0.92	1.50	2.06	0.99	Mean of the Differences of		
15	0.94	1.36	1.74	1.22	Experimental	−0.84	−1.16
16	0.90	1.92	2.90	1.28	t	3.71	0.98
					p	$<.01$	.40
Av.	0.91	1.51	2.05	1.20			
RAP Av.	149	184	178	133			
mm. Hg S.D.	±17	±14	±19	±23			
P.P. Av.	38	62	21	37			
mm. Hg S.D.	±7	±16	±4	±10			
RAP/FEM							
Av.	0.97	1.29	1.36	1.08			
S.D.	±0.04	±0.13	±0.17	±0.13			

in stage 2 with stage 1). On the other hand, significant increases in sodium excretion and urine volume result when mean pressure is increased in every case ($p = 0.01$ for sodium and $p = <0.01$ for urine volume). Since these increments occurred with little or no increase in filtration rate, the question is opened again as to whether the increase in sodium excretion is due solely to increases in sodium load to tubular cells which reabsorb a constant amount, or whether the calculated decrease in percentage of load reabsorbed results from some other influence set into play by the increase in arterial pressure.

Discussion

It has been shown in the present experiments that decrease in pulse pressure does not influence renal plasma flow as measured by the paraaminohippurate clearance whether this alteration is made at normal, reduced, or elevated mean pressure. Similar findings were made by Ritter[10] who measured renal blood flow continuously with a rotameter. These findings confirm the earlier conclusion of Gesell[6] on the effects of decrease in pulse pressure on blood flow. Nor was filtration rate altered in any way by reduction of pulse pressure. Sodium excretion and urine volume were unmodified by reduction in pulse pressure at normal and decreased mean pressure, contrary to the findings of Gesell. The reason for this difference in results cannot finally be decided upon, but emphasis is here placed on the necessity for rigid control of experimental kidney modifications with simultaneous control observations of the opposite kidney to eliminate the possibility of nonspecific factors influencing electrolyte and water excretion. Thus, in two of the experiments reported by Gesell the control kidney was not functioning; in a third, a change was noted when the damping chamber was connected both in the experimental and control kidney, although not of the same magnitude. Finally, another experiment is recorded in which urine flow diminished with *increase* in pulse pressure rather than decrease.

As disclosed in earlier reports[1, 2, 11, 12] renal blood flow and filtration rate exhibit striking autonomy in the face of both decrease and increase in mean arterial pressure. Evidence has been advanced that this control is by adjustment of the afferent arterioles.[1, 11] Yet despite this constancy of blood flow and filtration rate, the excretion of sodium and water are disproportionately influenced with marked percentile decreases in excretion paralleling decreases in mean pressure, and marked increases paralleling increases in mean pressure. Dismissing for the moment the possibility that small changes in sodium load may cause large percentile changes in sodium excretion and accepting the conclusion that changes in pulse pressure are without effect, we may consider possible mechanisms whereby alteration in perfusion pressure per se may modify electrolyte and water reabsorption by the tubules.

One possibility is that the perfusion pressure directly controls the rate of movement of the glomerular filtrate through the tubular lumen and inversely influences the time for reabsorption of sodium and water. (It is assumed that sodium reabsorption controls water reabsorption in the present discussion.) It would appear that this would operate only if the constancy of filtration rate resulted from opening and closing new nephron circuits. On the other hand, if all nephron circuits are functional and the constancy is maintained by adjustment of the afferent arterioles, then filtration pressure should remain constant as would the rate of movement of tubular urine. Present evidence favors the latter alternative.

Swann and Prine[7] have demonstrated that renal interstitial pressure varies directly with the arterial pressure. If this relationship proves to be correct, one may at least speculate on an alternative explanation. It is possible that elevation of renal interstitial pressure impedes the diffusion of ions from tubular cells to blood and raises the concentration gradient against which sodium and water need to be reabsorbed. Conversely, when arterial pressure is decreased, reabsorption is favored for opposite reasons. A similar view has been proposed by Shipley and Study.[12] This view would be strengthened by the finding that other substances absorbed by the tubular cells are influenced in a similar manner.

An obstacle to the hypothesis is the fact

that elevation of renal venous pressure also favors sodium retention,[13, 14] but is accompanied by increase in renal interstitial pressure.[8, 15] It has been proposed that the dominant factor favoring sodium retention with this experimental procedure is compression of the distal tubular system by the engorged venous radicles. This may slow movement of urine and also build up intraluminal pressure so that a favorable diffusion gradient is again re-established.

Blake and associates[3] and Mueller and coworkers[4] also observed reduction in sodium excretion and urine volume with constancy of filtration rate with moderate compression of the renal artery. Unfortunately, in neither study were pressures measured distal to the compression, but it is certain that both mean pressures and pulse pressures must have been reduced, and that filtration rate and blood flow were maintained by mechanisms discussed above. Mueller and associates take the rather extreme view that the changes in sodium excretion are in response to exquisite control of glomerular filtration, whereby changes too small to show up with present methods of measurement cause palpable reduction in sodium excretion. This opinion ignores the possibility that other hemodynamic factors may be operative in influencing tubular reabsorption. In the present experiments a very obvious correlation exists between mean arterial perfusion pressure and sodium and water excretion, and offers an alternative direction in which to seek for an explanation for changes in sodium excretion and urine volume which may go on without apparent alteration in filtration rate.

Summary

1. Decrease in pulse pressure has no influence on effective plasma flow (paraaminohippurate clearance), filtration rate (creatinine clearance), sodium excretion, and urine volume when altered at normal, reduced, or elevated mean renal arterial pressure in dogs.

2. Plasma flow and filtration rate exhibit constancy in the face of decrease in mean perfusion pressure from averages of 149 mm. Hg to 88 mm. Hg, or increases to 184 mm. Hg. However, decrease in pressure is accompanied by large percentile decreases in sodium excretion and urine volume, and increase in pressure results in large percentile increases in excretion of sodium and water. Changes in sodium excretion and urine volume are always proportional.

3. Possibilities are considered as to whether the changes in sodium excretion and urine volume are due to small alterations in sodium load resulting from minor changes in filtration rate, or whether some other hemodynamic factor such as renal interstitial pressure may influence sodium and water reabsorption. The latter may act by changing diffusion gradients in the interstitial spaces of the kidney.

Acknowledgments

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The Determination of Cardiac Output by a Continuous Recording System Utilizing Iodinated (I^{131}) Human Serum Albumin

I. Animal Studies

By William J. MacIntyre, Ph.D., Walter H. Pritchard, M.D., Richard W. Eckstein, M.D., and Hymer L. Friedell, M.D.

A method is outlined for the determination of cardiac output by the injection of iodinated (I^{131}) human serum albumin and continuous recording of the dilution curve. The calibration of the flow system by means of the final dilution and blood volume is discussed along with the possible application to an external measuring method. The results of eight dilution curves obtained from dogs are presented and the calculated cardiac outputs compared with the values measured by the rotameter method.

ESTIMATION of cardiac output by the injection method has been described by Kinsman, Moore, and Hamilton,[1] using dye, and by Nylin and Celander,[2] utilizing radiophosphorus-tagged red cells. In this method the dilution of the injected substance as a function of time is determined. Since the resultant dilution curve is necessarily dependent upon the volume of flow, the cardiac output in terms of liters of flow per unit time may be estimated.

In both these methods the dilution is determined by serially sampling arterial blood at short time intervals. In the first method the dilution may be determined colorimetrically and in the second method by beta particle assay methods. With the successful use of iodinated (I^{131}) human serum albumin in determinations of blood volumes[3, 4] the possibility of a continuous recording of the dilution curve utilizing gamma ray assay methods seemed feasible. There would be several advantages to such a method: (1) the serum could be used directly with no incubation required; (2) the absorption of gamma rays in small thicknesses of tissue is negligible so that a direct reading of the activity in the blood can be made during the time it is flowing; and (3) accurate timing of the dilution curve is more easily obtainable.

From the Atomic Energy Medical Research Project, and Departmemt of Medicine, School of Medicine, Western Reserve University, Cleveland, Ohio.

This work was performed under A. E. C. Contrat No. W-31-109-eng-78 with Western Reserve University.

Method

Approximately 100 μc. of iodinated (I^{131}) human serum albumin were injected in the jugular vein of open chest, heparinized dogs weighing 10 to 25 Kg. The right femoral artery was cannulated into a rubber tube of about 3 mm. diameter, and this rubber tubing fixed over a gamma detector of high sensitivity. Blood was allowed to flow through the tube into an open beaker, with the rate of flow adjusted by a screw clamp to approximately 30 cc. per minute, or was re-led into the distal portion of the proximally cannulated femoral artery. The inscribed curves and calculated outputs were essentially unchanged by this procedure. The dilution curve was obtained by plotting the radioactivity of the blood flowing over the detector as a function of time. This curve was recorded automatically by an Esterline-Angus Graphic Meter, but as the counting rate responded logarithmically, the curve was redrawn to a linear scale for an accurate representation of the dilution. The absolute activity was then determined by calibrating the flow system with a known concentration of I^{131} solution. The calibration method chosen for the following work involved the determination of the final dilution (blood volume) by withdrawing an arterial sample of whole blood 10 minutes after the iodinated (I^{131}) human serum albumin was injected. The specific activity of the whole blood was measured in vitro in terms of μc. per cc. and the flow system calibrated by ob-

servation of the response of the system in vivo to this known activity at final dilution. This is then the response of the gamma detector to a known concentration of activity in terms of counts per minute per μc. per cc. A schematic diagram of the experimental setup is shown in figure 1.

Equipment

With application of this method to humans, specific activities as low as 0.02 to 0.03 μc. per cc. were anticipated. As the volume sampled in the flow stream is about 0.7 cc. the total activity present would be too low for successful gamma assay by a Geiger counter. For this reason a scintillation counter of a type previously described[5] was used. This counter exhibited a sensitivity to gamma radiation of I^{131} of about fifty times the sensitivity of a conventional brass-wall Geiger counter.

For recording the activity passing through the rubber tubing as a function of time the conventional counting rate meter is not satisfactory because of the memory effect, in which the count at any time is influenced by the previous count recorded.[6] This can be compensated for by allowing sufficient time for the rate meter to reach equilibrium, but such time is far in excess of the time of the normal dilution curve. To overcome this difficulty a Berkeley Counting Rate Computer Model 1600 was used in conjunction with a scaler and Esterline-Angus Graphic Meter. The computer is activated by the resultant pulse from a scaler after the collection of a predetermined number of counts. As each reading is a measurement of the time to collect this predetermined number of counts, each reading is completely independent of any previous reading.* The chart speed of the Esterline-Angus Graphic Meter was set at 12 inches per minute. From this base line the response of the concentration was fixed in time with sufficient data readings taken during the 20 to 40 seconds of the primary circulation to determine the dilution curve.

Calculation of Cardiac Output

The general shape of the dilution curve and the equation describing the primary circulation have been fully discussed in previous works,[1, 2] and are illustrated in figure 2. Both methods utilize an extrapolation of the descending curve before recirculation begins, as shown by the dotted line of figure 2, and both derive an expression relating the injected activity to the concentration and flow during the time of the primary circulation. The quantity of injected material, I, may then be expressed as the product of the concentration, c, and the

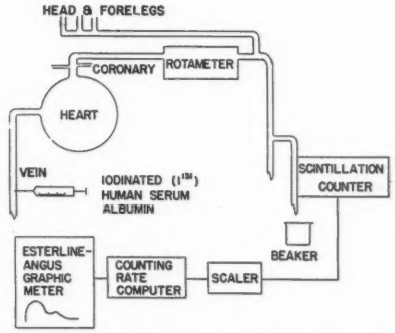

Fig. 1. Schematic diagram of experimental set-up for simultaneous determination of cardiac output by rotameter and injection methods.

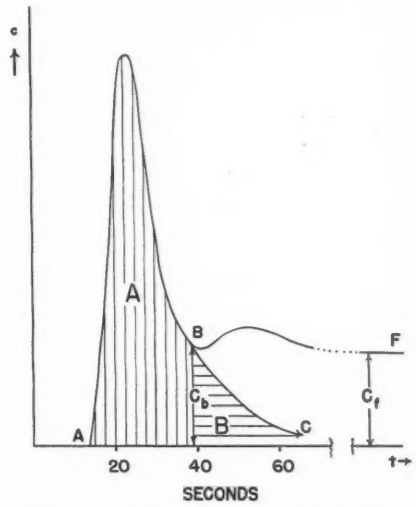

Fig. 2. General form of dilution curve.

rate of flow, F, integrated over the entire time:

$$I = \int_0^\infty cF\,dt$$

Provided the rate of flow, F, is considered to be constant, the following expression may be used for its solution:

$$F = \frac{I}{\int_0^\infty c\,dt}$$

* A complete description of the counting rate computer is given in the manual of operation for this instrument. Berkeley Scientific Company, Richmond, Calif.

where $\int_0^\infty c\,dt$ is the area under the primary circulation curve and dotted extrapolation line. This area may be expressed as the area A, measured by a planimeter, and the area B calculated by the formula:

$$B = \int_0^\infty c_b e^{-\lambda t}\,dt = \frac{c_b}{\lambda}$$

where c_b is the value of the concentration at point B and λ is the constant determined by plotting the logarithm of the concentration along the line BC of figure 2 against time.

This reduces the expression to:

$$F = \frac{I}{A + B}$$

The concentration, c, was determined as outlined previously by comparison of the known activity of the final arterial blood dilution at 10 minutes as measured in vitro with the response of the detector to the same dilution at the final part of the curve at the same time. This is shown as point F on figure 2. Since the injected dose, I, is equal to the product of the circulating blood volume, V, and the specific activity of the final dilution, c_f, we may write:

$$F = \frac{c_f}{A + B} V$$

Since the first term on the right is a ratio, it is seen that the specific activity at final dilution, c_f, may be expressed in terms of counts per minute at point F and the dilution curve expressed with an ordinate of counts per minute. This is important in the application to any external counting method since the final value of the dilution curve may calibrate the flow system when other means would be extremely difficult.

To look at this descriptively, the above expression may be rewritten with a substitution of the product of the average concentration, c_{av}, and the time, T, of the dilution for the area, $A + B$. Now as the final dilution, c_f, shows the concentrations obtained when diluted by the total blood volume, the ratio $\frac{c_f}{c_{av}}$ shows what fraction of the blood volume must have been ejected by the heart during time T. Output per unit time is then obtained by dividing by T:

$$F = \frac{c_f}{c_{av}} \frac{V}{T}$$

This is similar to the equation used by Kinsman, Moore, and Hamilton.[1]

Results

Simultaneously with these determinations the cardiac output was determined by an optically recording rotameter* inserted into the thoracic aorta just distal to the arch.[7] The vessels arising from the aortic arch proximal to the rotameter were ligated and cannulas inserted into their distal ends. Flow to these areas was incorporated into the total metered flow (cardiac output) by connections to the outflow side. By this technic total cardiac output except for coronary flow was measured. The results of both methods are shown in table 1, and typical dilution curves by figures 3 to 6.

Table 1. *Cardiac Output.*

Exp.	Dilution Method cc./min.	Rotameter Method cc./min. (as measured)	% Deviation	Rotameter Method cc./min. (with 5% added for coronary flow)	% Deviation
1.	1670	1385*	21*	1454*	15*
2.	1220	1105	10	1160	5
3.	1245	1110	12	1165	7
4.	1960	1750	12	1838	7
5.	1470	1230	20	1292	14
6.	960	835	15	877	9
7.	1930	1748	10	1835	5
8.	2210	1874	18	1968	12
Average deviation			+15		+9

* The major vessels in the upper thorax were ligated and the head was supplied through the left common carotid only.

The dilution method averaged values about 15 per cent higher than the recorded corresponding values obtained on the rotameter, with a variation between 10 per cent higher

* Expenses for the rotameter experiments were defrayed by a grant to Dr. Richard W. Eckstein from the Cleveland Heart Society.

and 21 per cent higher. Part of this deviation is due to the fact that the rotameter did not measure the coronary flow and, in experiment 1, probably a small portion of the head flow.

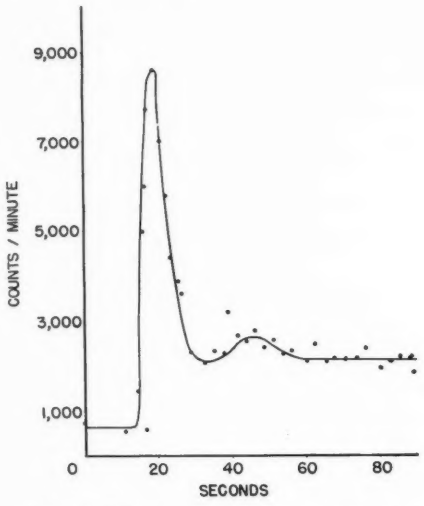

FIG. 3. Dilution curve for experiment 2.

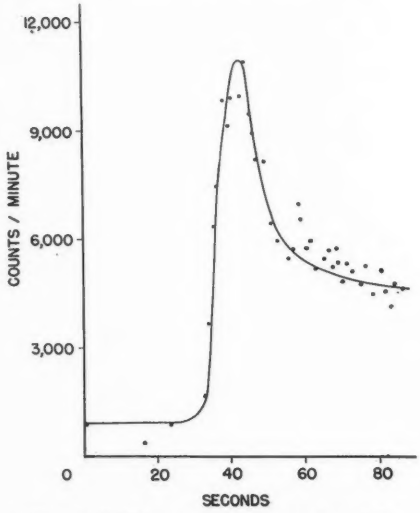

FIG. 4. Dilution curve for experiment 3.

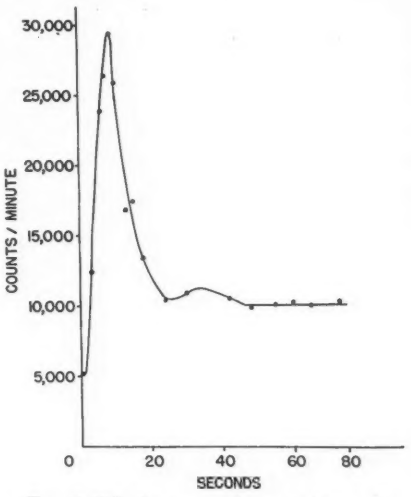

FIG. 5. Dilution curve for experiment 5.

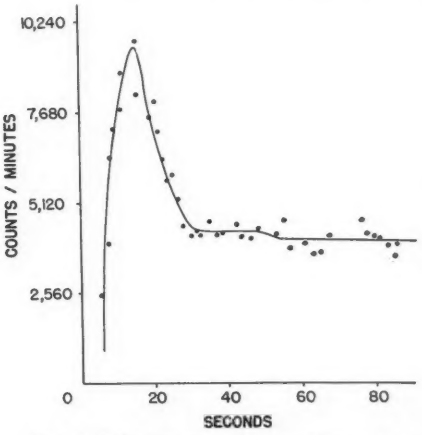

FIG. 6. Dilution curve for experiment 6.

TABLE 2.—*Cardiac Output*

Exp.	Dilution Method (Fast Tube Flow)	Rotameter Method	Exp.	Dilution Method (Slow Tube Flow)	Rotameter Method
	cc./min.	cc./min.		cc./min.	cc./min
3	1245	1110	3a	791	1850
4	1960	1750	4a	1210	1620

Although the coronary flow is usually taken as 5 per cent of the cardiac output, Eckenhoff, Hafkenschiel, and Landmesser[8] have pointed out that this proportion can be much higher (perhaps to 10 per cent or more) when the circulation is depressed. Even assuming only a 5 per cent addition for coronary flow the agreement is still within 9 per cent, which is within the 11 per cent estimate for the dilution method by Werkö and co-workers.[9] Since

the error is always on the high side, however, it is possible there is a small systematic error in the method.

In the procedure used, no phase was critical except that of insuring a sufficiently rapid flow of blood through the rubber tubing. When this flow was constricted sufficiently (approximately 5 cc. per minute), a slow dilution curve (and consequently a low output) was obtained. This was considered to be due to a stagnation of the blood in the tubing, resulting in a broader dilution curve which was falsely recorded as a slow circulation in the animal. This effect was checked by taking two successive runs on each of two dogs, one with slow tube flow and one with fast tube flow, and comparing the results with the rotameter outputs.

As seen in table 2 the fast flow gives a close correlation with the rotameter values while the slow flow does not. Provided the flow is fast enough to prevent pooling in the tube, the rate of tube flow should have no effect on the output.

Since no other difficulties were encountered and since the over-all correlation appeared satisfactory, further work is anticipated applying this method to man. In this case, correlation will be obtained by means of the Fick method.

Summary

Iodinated (I^{131}) human serum albumin has been injected into the jugular vein of dogs and a continuous record of the dilution obtained as a function of time. The cardiac output from these curves has been calculated from the derived formula and compared with values obtained from the rotameter method run simultaneously. The comparison of these two methods has been found to agree within 9 per cent.

Acknowledgment

The authors wish to acknowledge the assistance of Mr. William C. Schmidt in the recording and calculation of the dilution curve and of Drs. William Newberry and James McEachen for the technical assistance in the rotameter operation.

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Macrophage Migration in Experimental Atherosclerosis

By JOHN H. SIMONTON, M.D. AND JOHN W. GOFMAN, M.D.

With the object of testing the importance of macrophage transport of lipid in the production of atheromas, a radioisotope was employed in labeling reticuloendothelial cells. Rabbits were injected with this isotope, and lipemia induced by cholesterol feeding. Subsequently the animals were sacrificed and the distribution of the label determined. High concentrations of the label were found in Kupffer cells, in splenic and marrow macrophages, but no significant increase was demonstrated in aortic atheromas. This finding is interpreted as evidence against the macrophage theory of genesis of atherosclerosis.

THE source of the lipid material occurring in atheromatous lesions has been attributed to: (a) local fatty changes; (b) movement of lipid-bearing blood macromolecules into the arterial intima; (c) movement into the intima of lipid-filled cells which have originated elsewhere in the body.[1]

The present study represents an attempt to evaluate the last hypothesis, specifically with reference to the migration of Kupffer cells from the liver through the circulation to the aorta.

Means of concentrating radioisotopes in liver, spleen and bone marrow were available to the authors in this laboratory.[2] It was strongly suspected that the colloidal vehicle employed was taken up by the cells of the reticuloendothelial system existing in these tissues. That this is, in fact, the case has been shown in the present work. If a representative number of liver macrophages were thus labeled, and if they migrated to the aorta during the course of cholesterol feeding to rabbits, then a relatively great increase in radioactivity would be expected to appear in the aortic plaques. Conversely, if the activity in the diseased aortas of cholesterol-fed rabbits failed to exceed that appearing in control animals, it was felt that strong evidence against macrophage migration, as a mechanism in this disease, would have been adduced.

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METHODS

A. The production and morbid anatomy of cholesterol-induced rabbit atherosclerosis has been so thoroughly described in the literature that they require little repetition here.

Young white rabbits ranging in weight from 2035 to 3460 Gm. were divided into two groups, both of which received the radioactive isotopes, while only one was fed cholesterol.

Albers Rabbit Family Ration was ground, mixed with crystalline cholesterol, and the resulting powder made into tablets. Calcium stearate and powdered sugar were added in small amounts to improve the cohesiveness of the tablets. This special diet was administered on alternate days so that each animal received an estimated 3 Gm. of cholesterol per week. After a one or two day period of sluggish eating, the rabbits were found to consume the tablets readily. The special diet was supplemented with the stock chow, carrots, greens, water and salt ad libitum. All the animals were found to gain weight on this regimen. No external signs of cholesterol toxicity were observed over the experimental period.

The control animals received an identical diet with the exception of the Albers-cholesterol mixture.

B. Thorium 230 (ionium*) was used as the tracing isotope. It was injected intravenously in a colloidal citrate-hydroxy vehicle[2] previously employed in localizing certain other radioisotopes in liver, spleen and marrow.[3]

Five of the animals received their colloid in

* Ionium: a radioactive isotope of half-life 8.3×10^4 years, emitting alpha particles of 4.66 mev (million electron volts), and having a range in air of 2.85 cm (in the NTA-plate emulsion, of about 20 microns).

divided doses in order to label a maximum number of macrophages.

C. The distribution of the radioactivity was determined by autographic methods and checked by radioassay of the critical organs. The animals were sacrificed at intervals determined by the length and amount of cholesterol feeding and by the state of the serum.

Samples of liver, spleen, marrow, lung, adrenal, aorta, and when present, atheroma, were taken from each animal and imprint preparations made upon nuclear track plates.* These plates were thus exposed to the alpha radiation present in the tissue and developed at successive intervals of time. (The number of tracks present will increase with time following the basic radioactive decay law.) After development, rinsing, fixing, and washing of the plates, the tissue adhering to the emulsion surface was stained either with Jenner-Giemsa or with Oil Red O and Harris Hematoxylin, and the plate examined microscopically.

The alpha tracks were manifested as short, linear rows of exposed silver grains occurring as occasional tracks or dense bursts. The rays are emitted from the parent atoms through a 4π solid angle and for a reasonably complete count it is necessary to observe several focal planes through the emulsion.

This technic has the advantage of a minimum of steps during which radioactivity might be lost, and the all-important advantage that many cells will be sufficiently removed from their neighbors so that precise localization of the alpha bursts can be made. It has the disadvantages of some loss of tissue in the development process as well as some deterioration of tissue during the weeks of exposure prior to fixation and staining. Clumping of tissue occurs also, so that dense, unresolvable masses of cells and tracks are found. However, it was felt for the purposes of this experiment that the advantages of the method outweighed its deficiencies (figs. 1, 2, and 3).

Ordinary tissue radioautographs made by ex-

FIG. 1. Photomicrograph made from a liver imprint upon an NTA plate. Note hepatic cord cells and adjacent Kupffer cell with its concentration of alpha tracks. This plate was exposed seven days; stained with Jenner-Giemsa. Oil immersion. Rabbit 58.

FIG. 2. Three cord cells are shown with a macrophage. Note "beads" of India Ink beside the nucleus of the macrophage. Exposed for 46 days; stained with Jenner-Giemsa. Rabbit 51.

* Kodak-NTA: emulsion thickness—25 microns; surface area—1 by 3 inches; recording alpha particles, protons and deuterons.

posing histologic sections to the emulsion were tried but it was found that cells were too closely packed for definite matching with emitted alpha tracks.

Tissues surviving best through photographic development were the densely cellular ones: liver, spleen and marrow. The normal architecture of lung alveoli and aortic intima was not preserved in the imprint preparations. Attempts were made to obtain isolated foam cells but a reproducible technic was not found.

FIG. 3. The same liver cells shown in figure 2, but photographed in a deeper focal plane. Note α tracks.

Fatty material was expressed through razor cuts made into fresh aortic plaques and deposited upon the emulsion surfaces of NTA plates. This material subsequent to the development of the plate was stained with Oil Red O and Harris Hematoxylin, and studied for associated alpha tracks.

Formalin-fixed aortas were cut on the freezing microtome into strips five to seven microns thick. These were floated upon the NTA plates which were then allowed to expose. The formalin in which the tissue was fixed and the water in which the strips were floated were tested and found to contain a negligible amount of radioactivity. These "strip" preparations took a fat stain and retained sufficient structure to permit identification of plaque areas and to serve as a check on the direct imprint preparations (figs. 4 and 5).

Routine counts were made of the tracks occurring on liver and aorta plates. Typical results are recorded in tables 2, 3, and 4.

Samples of six organs were removed from each animal, weighed, wet-ashed, reduced to volume, and an aliquot mounted on platinum disks and assayed for alpha radioactivity. Because of the limited amount of diseased aorta it was not practicable to assay pure plaques; therefore, the figures reported for aorta represent parts rich in (60 to 80 per cent of the intimal surface) but not exclusively made up of atheromas (table 5).

FIG. 4. A "strip" (see text) preparation mounted on an NTA plate. Plaque tissue is visible above the media. Oil Red O and Harris Hematoxylin. 27 days exposure. Low power. Rabbit 78.

Each animal received between 1 and 2 cc. of India ink within the last 24 hours of survival. This facilitated the identification of macrophages and incidentally demonstrated that phagocytic function of the macrophages had not been impaired by the presence of radioactivity throughout the feeding period.

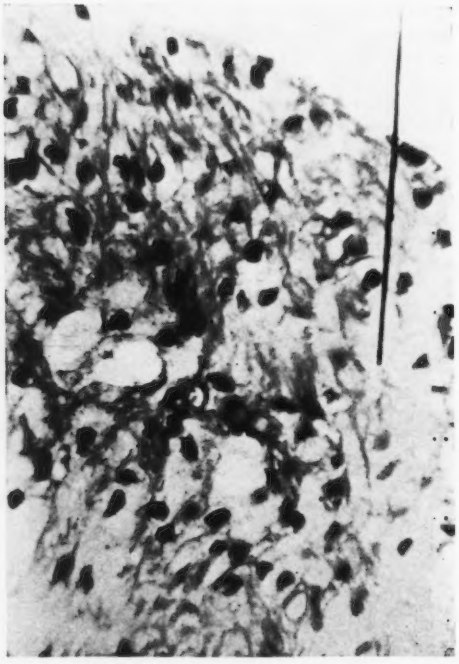

FIG. 5. Histologic section made through plaque tissue contiguous to that used for the strip preparation shown in figure 4. Note foam cells. Hematoxylin and triosin. High power. Rabbit 78.

TABLE 1.—*General Data*

No.	Weights (Gm.)		Est'd. Cholesterol Intake (Gm.)	Duration Feeding Period (days)	Serum Total Cholesterol Levels (mg. %)		Dose of Io(cc).	Severity of Lesions
	Initial	Terminal			Initial	Terminal		
50	3385	4985	88.5	210	19	230	0.25	Minimal
51	3460	4550	73	190	63	720	0.50	Moderate
52	3950	4725	111	235	23.5	—	0.50	Minimal
53	2900	4365	69	149	22	467	0.25	Moderate
55	2620	4200	65	150	57	770	0.25	Severe
78	2815	4670	61	147	—	368	0.25	Moderate
54	2660	4790	87.5	208	22	109	0.50	None
56	3120	5485	0	214	—	—	0.25	Control
57	2035	3925	0	122	—	—	0.25	Control

An occasional liver-imprinted NTA plate was fat-stained. While detail was poor, sufficient structure remained so that cord and Kupffer cells could be distinguished and cytoplasmic sudanophilism of both cell types observed. Fat-stained histologic sec-

TABLE 2.—*NTA Plates: Liver-Imprint Preparations*

No.	Kupffer cells with bursts of 3 or more α tracks	Mean Number of Tracks/Cell	No. of Cells Counted	Exposure Time
	%			*days*
51	79	10 (range: 0–43)	226	53
52	80	14 (range: 0–60)	151	31
53	87	10 (range: 0–38)	158	53
55	84	12 (range: 0–60)	135	74
78	71	5 (range: 0–50)	125	25
56	81	10 (range: 0–48)	70	51
57	84	12 (range: 0–70)	113	36

Explanation: 56 and 57 are controls; they received the radioisotope but no cholesterol.

TABLE 3.—*NTA Plates: Aortic Imprint Preparations*

No.	Tissue Areas*	Maximum Burst No. of Tracks	Occurrence	Exposure Time
				days
51	Alpha track density within Bg† limits	5	once	59
53	Alpha track density within Bg limits	1	four times	53
55	"	3	once	67
78	"	4	once	34
56	"‡	4	once	51
57	"	3	twice	36

* These areas were stained with Oil Red O and Harris Hematoxylin. Cellular elements were frequently observed but definition was not considered satisfactory.

† Background limits: the number of alpha tracks observed on oil-power scan of blank slides ranged from 24 to 49.

‡ 56 and 57 received the radioisotope only.

TABLE 4.—*NTA Plates: Aortic "Strip" Preparations*

No.	Plaque Area*	Alpha Tracks		Exposure Time
		Total	Bursts	
				days
51	a	1	none	22
	b	7	"	22
	c	15	3—once	41
	d	6	none	46
	e	19	2—twice	46
	f	10	none	53
	g	16	2—twice	53
52	a	44	2—three times	36
	b	32	2—once	36
78	a	10	2—once	36
	b	2	none	36
	c	6	"	28
	d	9	"	28
	e	7	2—once	57
	f	4	none	57
	g	6	"	57

* These plaques varied in length from $\frac{1}{4}$ to $\frac{1}{64}$ inches. Thus a plaque with longer exposure time might show fewer total tracks than a plaque with a shorter exposure but greater area. These plaques were studied under oil-immersion magnification. The track-density in the subjacent media was of the order of that of the intima.

DISCUSSION

We have found no evidence in microscopic preparations of aortic atheromatous tissue of the presence of "labeled" Kupffer cells, or of other labeled macrophages from spleen or bone marrow. The "label" consisted of the presence of *bursts* of three or more alpha tracks radiating from a central intracellular area. Radioautographs of splenic phagocytes showed an activity of the order of that associated with liver macrophages, while those of marrow macrophages exhibited considerably more.

The scattered single alpha tracks observed in the aorta preparations, as well as the occasional bursts of three, four or five tracks, were found to be strikingly fewer than those found in liver imprint preparations. If plaque tissue arises entirely or largely from migrated macrophages, we would be justified in expecting an activity *greater*, per gram of tissue, than that of the liver. It seems more probable that what little radioactivity is observed microscopically in aortic preparations and assayed in samples of aortic tissue represents phagocytosis of the colloidal vehicle *directly* from the blood stream by aortic cells.

TABLE 5.—*Specific Activity (Per Cent of Injected Dose Per Gm. of Tissue)*

No.	Aorta	Liver	Lung	Adrenal	Marrow	Spleen
50	0.012 ± .003	0.10 ± .01	0.016 ± .006	0.008 ± .002	0.21 ± .03	0.12 ± .02
51	Bg*	0.42 ± .01	0.007 ± .002	0.005 ± .002	0.11 ± .03	0.085 ± .035
53	0.009 ± .002	0.12 ± .02	0.029 ± .003	0.014 ± .003	0.33 ± .10	0.21 ± .01
54	0.013 ± .001	0.13 ± .01	0.010 ± .002	0.013 ± .002	0.59 ± .04	0.32 ± .03
56	Bg*	0.09 ± .01	0.007 ± .002	0.016 ± .004	0.19 ± .03	0.11 ± .01
57	0.022 ± .007	0.35 ± .02	0.11 ± .01	0.089 ± .015	0.90 ± .18	0.52 ± .06

* Background: in these two instances, the radioactivity of the samples was so low as not to differ significantly from "background" radiation.

Explanations: (1) Nos. 50, 51, 53, 54 were fed cholesterol.
(2) Nos. 50, 51, and 53 developed gross lesions. 54 failed to develop gross lesions.
(3) Nos. 56, 57 received the radioisotope only.

tions of livers from each of the atheromatous animals were made and showed fatty cellular changes and the presence of fat and India ink within the same Kupffer cells. Almost every Kupffer cell in a given field appeared to be fat and ink laden.

The possibility cannot be ruled out that "labeled" Kupffer cells may have undergone necrosis during the course of the experiment and their contents been scavenged by other

Kupffer cells. However, if these macrophages are stimulated by a continuous excess of liver cholesterol to release themselves into the blood stream and to migrate to the arterial intima, the presence of such "late"-labeled Kupffer cells might reasonably be expected in plaque areas.

Total liver radiation which the animals received over the four to six month experimental period, ranged from 0.25 rep to 0.5 rep.* Because of their concentration of the isotope, liver macrophages would, on the average, receive a dose of the order of 10 rep for the experimental period. However, macrophages showing far more than 10 tracks were still capable of engulfing India ink at the end of the experimental period indicating that their phagocytic function at least was not impaired by the radiation itself.

Kuntz and Sulkin,[4] injecting hypercholesterolemic rabbits with India ink and lithium carmine, found the dyes in visceral phagocytes but none in the foam cells of the atherosclerotic lesions. However, we felt that it was of prime importance to introduce a macrophage-labeling agent *prior* to the inception of cholesterol feeding in order to expose these cells to the processes of cholesterol metabolism. Thus, a foam cell already imbedded in the atheromatous lesion might be a phagocyte of extra-arterial origin but yet be unable to get access to the circulating dye once within the arterial intima.

* Roentgen equivalent physical

Summary

In order to test the macrophage-transport hypothesis of atheromatosis, rabbits were injected with a radioisotope which was demonstrated to concentrate in visceral macrophages. Cholesterol feeding was then instituted. At the end of the feeding period, the animals were sacrificed and the distribution of radioactivity between various organs and the atheromatous plaques studied. It was found that the amount of radioactivity in the plaques was relatively very low. It is felt that this indicates macrophage migration is not a significant source of the foam cells in rabbit atherosclerotic lesions.

Acknowledgment

The authors wish to express their gratitude to Miss Anita Syrek for her valuable assistance in preparing tissues.

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Peripheral Vasomotor Effects of Adrenaline and Noradrenaline Acting upon the Isolated Perfused Central Nervous System

By ROBERT D. TAYLOR, M.D., AND IRVINE H. PAGE, M.D.

The problem of the participation of the nervous system in the control of blood pressure has received scant attention. Our purpose was to learn more of the nervous mechanisms which participate in its control. By means of a special technic which allows the brain to be perfused with blood from another animal and yet be connected with the body only by the nervous system, it was shown that pressor substances perfused through the brain cause a fall in pressure in the body. On the contrary, substances which are depressor in the donor's body cause a rise in pressure in the recipient's body when they act on the brain. We conclude that the brain contains hitherto unrecognized chemoreceptors independent of the carotid sinuses. Baroreceptors were not found in the blood vessels. This cerebral buffer mechanism must have important functions in determining the response to vasoactive substances, especially in hypertension and shock.

THE CONTRIBUTIONS of the central nervous system to the maintenance of arterial blood pressure are poorly understood. Least well known are the remote peripheral effects, mediated by nerves as the result of action of vasoactive substances on vasomotor centers. For instance, adrenaline has been said to be depressor, pressor, and inactive when circulated through the brain. Oliver and Shafer[1] in 1895 first considered it to have a central action and suggested that simulation of the vasodepressor center by adrenaline might account for the fall of blood pressure observed following its intravenous injection. Experimental support for this was furnished by Hartman, Kilborn and Fraser[2] and Gayet, Gayet and Guillaumie.[3] They reported vasodilatation in perfused limbs of dogs which were connected to the animal only by nerves when adrenaline was injected intravenously into the body. Cyon[4] and Tournade[5] used similar preparations but concluded that peripheral vasoconstriction rather than vasodilatation was induced by adrenaline which circulated through the central nervous system.

Pilcher and Sollman[6] perfused spleens which were separated from the bodies of the dog except for nervous connection. They found no change of splenic volume following administration of adrenaline to the body and concluded that the drug had no effects mediated through the nervous system. Anrep and Starling[7] perfused the brain by cannulating the basilar artery, noting peripheral dilatation when adrenaline was injected into the perfusing blood. Simultaneously, there occurred a rise of the blood pressure in the circle of Willis. They believed the hypertension resulted from vasoconstriction of the extracranial vessels which directed blood intracranially into the nonresponsive vessels of the brain. The peripheral vasodilatation they observed was then attributed to increased perfusion of the vasomotor centers rather than to the action of adrenaline as such.

Heymans and associates[8–10] perfused the isolated carotid sinus of an otherwise intact dog and also prepared animals so that the heads could be perfused by donor blood which did not reach the body of the recipient animal. In the latter experiments the only nervous connections which remained were the vagus nerves. Injection of adrenaline into the donor circulation caused bradycardia and fall of blood pressure in the body of the recipient animal. Since similar peripheral effects were brought about by sudden elevation of the perfusion pressure these workers attributed them to the

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rise of blood pressure adrenaline induced in the donor animals. The demonstration of such depressor reflexes led to the assumption that no central effects of adrenaline existed, although this was not shown by direct experimentation.

Subsequent to these studies, Tournade and Malmejac[11] and Gayet, Gayet, and Quivy[12] repeated their experiments with isolated perfused limbs but with the carotid sinus and the aortic depressor nerves destroyed. Vasodilatation was noted, although to a lesser degree than in their previous experiments.

These variant observations and conclusions probably are attributable to the fact that a satisfactory method had not been devised for direct perfusion of the head such that nervous connections are intact but that donor-head circulation and that of the body are entirely separate. The many attempts to develop such a method prior to 1932 disregarded the large intraspinal venous sinuses which extend the length of the spinal column just anterior to the cord, and permit free mixture of the blood of the body and donor-head circulation. Lewis[13] attempted to obliterate these sinuses by injecting them with liquid paraffin but made no provision to prevent interchange of blood through the intercostal arteries, so that his method was also unsatisfactory.

Nowak and Samaan[14,15] reviewed the history of efforts to perfuse the isolated nervous system and described a method which accomplished this in 1934. It depended upon: (1) exposing the cord by laminectomy at C-2, (2) opening the dura and retracting the cord to ligate the anterior spinal artery, and (3) obliterating the intraspinal venous sinuses with a U-shaped metal clamp placed below the cord. With this preparation they observed sharp reduction of peripheral blood pressure in response to centrally acting adrenaline when the carotid sinuses and aortic depressor nerves were intact. When the buffer nerves had been sectioned, adrenaline injected into the circulation of the recipient dog's head still caused vasodilatation in the body, although it was sometimes slight and inconstant. They concluded, as did Heymans, that the depressor effects of adrenaline injected into the cerebral circulation were primarily due to reflex responses of the carotid sinus mechanism to adrenaline hypertension of the donor dog. They believed that the depression noted after destruction of the buffer nerves occurred only because adrenaline hypertension of the donor animal perfused the vasopressor centers better and thus reduced peripheral vasomotor tone. In support of this concept, they perfused the dog's head with a pump and mechanically elevated the perfusion pressure which caused a fall of blood pressure in the body of the animal. However, they depended upon sectioning the nerve of Hering as it arises from the bifurcation of the carotid artery to inactivate the carotid sinuses and did not test the preparation for carotid sinus activity before pump perfusion.

During studies of the central effects of vasoactive drugs, we have developed a method for perfusion of the isolated nervous system which effectively separates the circulation of the body and head yet does not require release of cerebrospinal fluid or manipulation of the cord as in the method of Nowak and Samaan.

Methods

Two mongrel dogs were used in each of 127 experiments. The animals weighed from 6 to 15 kilograms. The donor dog was usually slightly larger than the recipient. Pentobarbital, 35 mg. per Kg., was given intravenously for anesthesia. A femoral artery of each dog was connected to a mercury manometer which recorded blood pressure changes on the smoked drums of two kymographs. Heparin was used as an anticoagulant both in the tubing leading to the manometers and for perfusion of the head of the recipient dog.

During preparation of recipient dogs, an infusion of 200 cc. of whole dog's blood was given. The dissection was carried out with an electrocautery unit and blunt dissection. With the dog on its back, a collar of skin 4 to 5 cm. in breadth was removed over the third to fifth cervical vertebrae. Both jugular veins, carotid arteries, and vagus nerves were isolated for a length of 8 cm. to 10 cm. and wrapped with moist gauze, both to prevent drying and to retract them from the field of operation. A segment of trachea was resected and the proximal end cannulated with a rubber cannula 40 cm. in length for connection to a respirator, if necessary.

Using the coagulating current, the cautery knife was used to cut the esophagus and neck muscles in a collar-like shape so that the fourth and fifth cervical vertebrae were exposed. Coagulation and contraction of the muscles controlled hemorrhage. The vertebrae

bodies were denuded of muscle by blunt dissection. With the dog on its belly a laminectomy at C-4 and C 5 was then performed. The articular facets were removed by ronguer to expose the vertebral arteries and veins. This usually caused brisk bleeding which could be controlled with muscle pledgets, coagulation, and finger pressure. The bone dissection was carried out so that the laminae and facets were removed flush with the vertebral body; otherwise a bridge of bone prevented complete occlusion of the anterior spinal veins by the wire snare which was applied.

By means of a flat, grooved, curved guide, which adapted to the contour of the spinal canal, a strand of No. 8 piano wire was passed beneath the cord. The wire was held in place with hemostats to prevent trauma to the cord while the two ends of the wire were threaded into a tonsil snare. This snare was used to tighten the wire firmly about the intervertebral disk, thus obliterating all vascular connections except those within the dura (figs. 1 and 2). Of these, the anterior spinal artery is the only one of appreciable size and it becomes imperceptible below C-3 since it is dissipated as large branches to the first three cervical nerve roots which were destroyed during the dissection of the neck muscles. Every effort was made to control bleeding points so that heparinized blood to be perfused through the dog's head would not escape during the course of the experiment.

The donor dog was heparinized by giving 4 mg. of heparin intravenously per kilogram of body weight. The anastomosis between the two dogs was limited to one carotid artery and one jugular vein of each dog. This was accomplished by appropriate sized plastic tubing previously filled with saline solution. When the circuit was functioning a clamp was placed on the remaining jugular vein and carotid artery of the recipient dog. The use of one vessel simplified the procedure and was quite adequate as evidenced by the continuation of respiration and the persistence of both corneal reflexes of recipient dogs after perfusion was started. Also cerebral anemia caused by clamping the perfusing artery caused sharp rise of the recipient dog's blood pressure much as complete and sudden cerebral anemia does in an intact animal. The carotid sinuses were inactivated unless otherwise indicated.

Injections were made into the arterial circulation through a three-way stopcock spliced into the circuit by a glass T tube. Whenever an intra-arterial injection is referred to in this paper it means this circuit. Adrenaline in doses of 0.01 mg., except as indicated elsewhere in the text, and noradrenaline, 0.01 mg., were used as standard in these experiments.

The completeness of the isolation was established by the failure of Evans Blue, given to the donor dog, to appear in the body of the recipient dog. Further, postmortem dissection showed no vascular communication between the head and body of the recipient animal.

Results

Effects of Adrenaline and Noradrenaline. Repeated injections of adrenaline and noradrena-

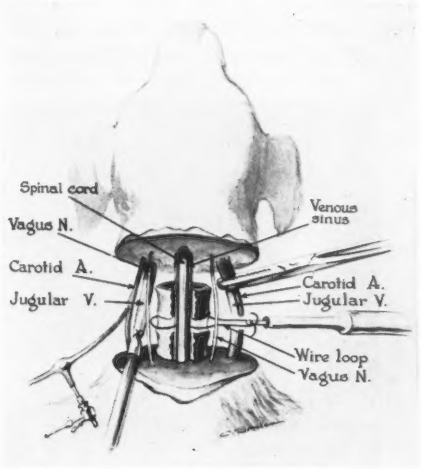

FIG. 1. Drawing of dissection necessary for perfusing the isolated central nervous system.

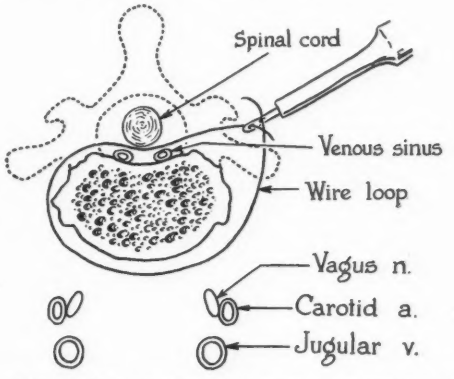

FIG. 2. Cross-sectional diagram of dissection in recipient dog.

line into the arterial circulation of the recipient dog's head caused an immediate and sharp fall of arterial pressure of the isolated body in each of the 127 experiments (fig. 3). The degree of fall varied widely from animal to animal (10 to 100 mm. Hg). In general, it depended upon the height of the control pressure in the recipient's body and the duration of the ex-

periment. Table 1 shows responses which occurred in 12 representative experiments. These were chosen to illustrate the greater fall of blood pressure which usually occurred when the recipient's body pressure was elevated. When the blood pressure was above 130 mm. Hg, adrenaline or noradrenaline usually caused the pressure to fall 50 to 100 mm. Hg. On the other hand, when the control pressure was

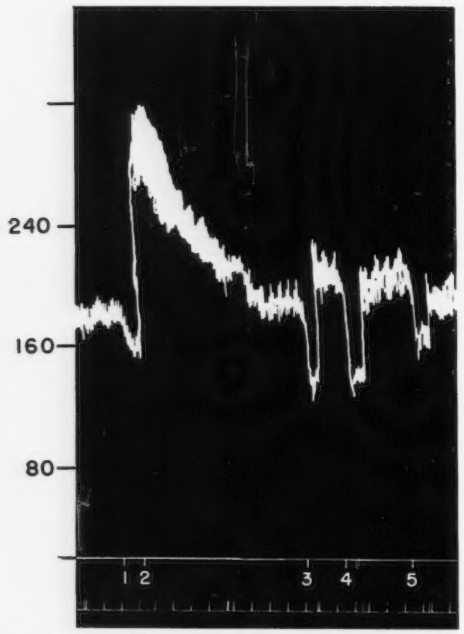

FIG. 3. Effects of injection of adrenaline into the perfusion circuit before and after destruction of the buffer nerves. *1.* 0.01 mg. adrenaline. *2.* Destruction of buffer nerves. *3.* 0.01 mg. adrenaline. *4.* 0.01 mg. adrenaline. *5.* 0.01 mg. noradrenaline.

lower the response was about 10 to 60 mm. Hg.

Preparation of each experiment took from three to four hours and the recipient animal was responsive for two to four hours thereafter. Early in the experiment the response of the recipient was greater and more brisk; after two or three hours the reactivity lessened. The corneal reflexes were then sluggish and it was difficult to maintain the arterial blood pressure of the recipient dog's body.

Animals that developed diarrhea, respiratory difficulties, or required large amounts of fluid during the period of dissection to maintain normal blood pressure, had relatively poorer responses than did more rugged animals.

The degree of depression of the blood pressure was roughly in proportion to the amount of pressor agent administered. For instance, 0.01 mg. of adrenaline given intra-arterially into the recipient's head reduced the body

TABLE 1.—*Interrelationship of Depressor Response of Recipient Dog's Body to Injection of Adrenaline and Noradrenaline into Arterial Circulation of the Head and the Control Blood Pressure of the Recipient's Body and Pressor Response of Donor Animal.**

Control	Blood Pressure in Body of Recipient Animal *mm. Hg*		Response of Donor Dog *mm. Hg*	
	Degree of Fall		Degree of Rise	
	Adrenaline	Noradrenaline	Adrenaline	Noradrenaline
212	−106	−98	0	18
176	−90	−72	14	18
170	−52	−54	18	22
164	−44	−42	8	16
148	−28	−22	10	18
142	−68	−58	14	20
140	−44	−38	12	14
132	−50	−44	14	28
128	−42	−46	34	42
120	−32	−40	16	28
114	−18	−4	12	30
112	−14	−12	14	24
108	−54	−60	0	24
92	−14	−16	10	50
84	−8	−12	10	14
80	−6	−8	4	18

* These responses were chosen from 12 different experiments to illustrate the greater response that usually occurs when the control pressure is high.

pressure 18 mm. Hg from a control level of 160 and caused a 10 mm. rise of donor dog's pressure, while 0.02 mg. of adrenaline reduced the recipient's body pressure 40 mm. Hg and caused a rise of donor's pressure of 20 mm. Hg.

Injections into the tubing leading to the head were much more effective than those given intravenously into the circulation of the donor dog. Further, the degree of depressor response of the recipient's body bore no relationship to the elevation of blood pressure these drugs produced in the donor. The re-

sponse of the recipient following intra-arterial injections into the cerebral circulation began before any drug reached the donor, and often there was enough dilution, at least of the small doses, to prevent change in the donor dog's pressure. Also, when the donor dog's blood pressure was elevated to similar levels by renin injections, the recipient dog's pressure showed slight, if any, change. Representative results are shown in table 2. Comparison is made of the effects of similar amounts of adrenaline and noradrenaline injected alternately into the recipient's head and intravenously into the donor body. The results show that the depressor response of the recipient's body is independent, to a large degree, of the pressor response of the donor.

In 6 experiments the effects of adrenaline and noradrenaline upon the peripheral circulation were tested by injecting the drugs into the cerebrospinal fluid. In 3 normal dogs, burr holes were made into the skull so the the tip of a needle could be passed into the lateral ventricle. Neither adrenaline nor noradrenaline had measurable effects upon the blood pressure when given in doses as high as 0.1 mg. In 3 experiments the drugs placed in the cisterna magna caused no rise of systemic pressure.

Effects of Change of Perfusion Pressure and Injection of Saline into the Carotid Sinus of the Recipient Dog. These were tested by injecting saline solution in amounts of from 1 to 25 cc., by varying the blood pressure of the donor dog, by bleeding until hypotension occurred, and by intra-arterial transfusions given under pressure to the donor dog. When the carotid sinuses of the recipient dog were denervated or cocainized none of these procedures affected the blood pressure in the body of the recipient animal. If the carotid sinuses were intact, the intra-arterial injection into the recipient's cerebral circulation of 1 cc. of normal saline usually had no effect and rarely caused a fall of the recipient's blood pressure. If 10 to 25 cc. of normal saline were rapidly injected into the carotid artery perfusing the head, peripheral pressure of the recipient dog usually fell 10 to 25 mm. Hg, while if a similar volume containing 0.01 mg. of adrenaline were injected the fall amounted to 40 to 50 mm. Hg (table 3).

In 4 experiments the arterial blood pressure within the carotid sinus of the recipient dog was varied widely by alternately bleeding the donor until hypotension (30 to 50 mm. Hg) occurred and retransfusing the blood into the donor dog's femoral artery under pressure, so that hypertensive levels were maintained (250 to 300 mm. Hg). These variations of perfusion pressure in the donor dog caused no significant change of arterial pressure in the body of the recipient dog.

TABLE 2.—*Depressor Effects of Adrenaline and Noradrenaline When Similar Doses Were Given Intravenously to Donor and Intra-arterially to Perfused Head.*

Control Blood Pressure		Response to Intravenous Injections to Donor *mm. Hg*				Response to Intra-arterial Injections to Perfused Head *mm. Hg*			
		Adrenaline 0.01 mg.		Noradrenaline 0.01 mg.		Adrenaline 0.01 mg.		Noradrenaline 0.01 mg.	
Donor	Recipient Body	Donor	Recipient Body	Donor	Recipient Body	Donor	Recipient Body	Donor	Recipient Body
120	110	46	−18	36	−38	16	−42	16	−50
134	130	40	−50	36	−10	14	−50	20	−28
146	132	40	−8	70	−14	26	−38	42	−48
128	90	26	−6	50	−12	10	−46	30	−40

TABLE 3.—*Effects of Injecting 25 cc. of Saline and 25 cc. of Saline with 0.01 mg. of Adrenaline into Carotid Sinus of Recipient Dog.*

Control Blood Pressure	Blood Pressure Fall after 25 cc. NaCl	Blood Pressure Fall after 25 cc. NaCl plus 0.01 mg. Adrenaline
mm. Hg	*mm. Hg*	*mm. Hg*
144	−10	−34
98	−10	−42
136	−12	−66
130	−8	−70
180	−22	−74

Effects of Excision of Carotid Bodies. Heymans[16] has shown that the carotid bodies act as chemoreceptors which reflexly influence respiratory and vasomotor centers in response to chemical agents circulating through them. To determine whether or not the carotid bodies were the site of action of adrenaline or noradrenaline which might have caused the de-

pressor effect we have observed, they were surgically removed by exposing the carotid bifurcation and excising them from 6 recipient animals 24 to 48 hours before the experiment. The depressor effects of centrally acting adrenaline or noradrenaline remained.

Effects of Section of Buffer Nerves and Excision of the Carotid Sinuses. After control responses to intra-arterial injections of adrenaline and noradrenaline were determined in 12 experiments, the carotid sinuses, aortic depressor nerves, and vagus nerves were successively inactivated, repeating the tests at each step. Initially, the left vagus nerve was cut, then the right aortic depressor nerve was isolated from the vagus and sectioned, followed by sectioning the remaining vagus nerve. The carotid sinuses were then exposed and inactivated by applying cocaine (10 per cent) solution. Three experiments are recorded in table 4. The central action of adrenaline and noradrenaline was not only present after the buffer nerves were inactivated but in some cases was enhanced.

In 10 experiments the carotid sinuses were denervated by cutting the nerves of Hering and stripping the sinuses of adventitia, or by complete excision of the sinuses four to five days before the experiment. The completeness of denervation in each case was demonstrated by the absence of blood pressure change, either when the carotid arteries were clamped separately, or following distention of them by intra-arterial injection of saline solution. Both vagus nerves were then sectioned. In most experiments this procedure caused a sharp elevation of blood pressure (fig. 3) due probably to the unopposed action of the sympathetic nervous system. These animals showed peripheral vasodepressor reactions in response to centrally injected adrenaline and noradrenaline. In some cases there was a greater response after the vagus and aortic depressor nerves were sectioned (fig. 3).

TABLE 4.—*Effects of Progressive Inactivation of Buffer Nerves upon Response of Recipient Body Blood Pressure to Centrally Acting Adrenaline and Noradrenaline.*

Procedure	Drug	Experiment No. 1		Experiment No. 2		Experiment No. 3	
		Initial B.P.	Depressor Response	Initial B.P.	Depressor Response	Initial B.P.	Depressor Response
Control	Adrenaline	114	−16	152	−26	120	−26
		92	−14	108	−32		
	Noradrenaline	132	−16	156	−30	110	−18
		90	−22	120	−40	130	−14
Left vagosympathetic trunk cut	Adrenaline	94	−24	138	−32	136	−38
						150	−58
	Noradrenaline	110	−22	164	−40	130	−40
Rt. aortic depressor nerve cut	Adrenaline	114	−34	170	−40	136	−70
	Noradrenaline	110	−22	166	−16	144	−56
Right vagotomy	Adrenaline	122	−12	170	−38	134	−64
	Noradrenaline	124	−12	168	−34	114	−60
Lt. carotid sinus cocainized	Adrenaline	134	−22	172	−30	138	−60
	Noradrenaline	126	−16	166	−26	104	−46
Rt. carotid sinus cocainized	Adrenaline	122	−22	200	−28	146	−58
	Noradrenaline	130	−50	184	−24	142	−52

Effects of Mechanical Elevation of Perfusion Pressure with a Pump. Our data suggest that the mechanical effects of perfusion pressure in the isolated head have little effect upon the peripheral blood pressure of the recipient dogs. However, Nowak and Samaan used a pump to mimic the pressure change adrenaline caused in the circulation of the isolated head after the buffer nerves were supposedly inactivated. Rise in perfusion pressure resulted in fall in arterial pressure in the recipient's body. They believed these changes occurred because of decrease of peripheral vasomotor tone resulting from better perfusion of the vasopressor centers. To explore

this apparent discrepancy 6 experiments were performed in which the isolated head was alternately perfused with a rubber tube pump and the arterial circulation of a donor dog. The carotid sinuses were intact in 3 of these

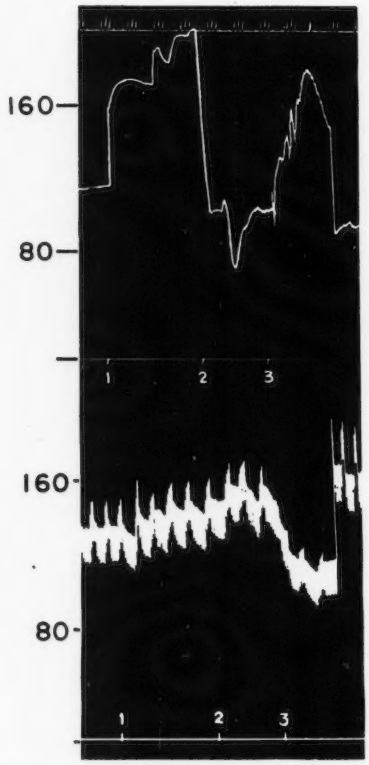

FIG. 4. Simultaneous record of blood pressure in recipient's cerebral circulation (upper tracing); in recipient's body (lower tracing). *1.* Elevation of cerebral perfusion pressure by means of a pump. No significant change in arterial pressure of the recipient's body. *2.* Change from pump perfusion to perfusion by a donor dog. *3.* Adrenaline (0.01 mg.) given into circulation perfusing the recipient's head. A fall in blood pressure occurs in the recipient's body.

dogs and inactivated in the other 3. The vagus nerves of all 6 were cut. The pump delivered blood from the right carotid artery of the donor dog and when not functioning the donor's left carotid perfused the recipient's head. Pressure changes within the head were measured by manometer recording the retrograde arterial pressure as present in the cephalic end of the clamped carotid artery of the recipient dog.

When the head was perfused by pump, the rate of flow was adjusted so that the level of this retrograde pressure was the same as when the heart of the donor dog provided the perfusing force. The flow was then increased so that the changes of arterial pressure within the head mimicked, as nearly as possible, those produced by intra-arterial injections of adrenaline and noradrenaline (fig. 4). Afterward, the pressure was elevated as high as the pump would permit (84 to 188 mm. Hg).

TABLE 5.—*Example of Peripheral Effects of Hypertension Induced by Pump and by Injection of Adrenaline and Noradrenaline into the Perfusion Circuit of Recipient Dog's Head.*

Stimulus	B.P. Changes in Head Measured in Opposite Carotid Artery	Net Change	Fall of Peripheral Blood Pressure in Recipient Dog	Net Change
	mm. Hg		*mm. Hg*	
Adrenaline 0.01 mg.	36 to 54	+18	108 to 74	−34
Noradrenaline 0.01 mg.	34 to 48	+14	104 to 74	−30
Pump	34 to 94	+60	118 to 104	−14
Adrenaline 0.01 mg.	28 to 40	+12	184 to 132	−52
Pump	32 to 90	+58	176 to 160	−16

In those animals in which the carotid sinuses were denervated, mechanical elevation of the perfusion pressure had no influence upon the recipient dog's peripheral blood pressure, while adrenaline and noradrenaline elicited prompt vasodepressor effects. Further, in those animals having functioning carotid sinuses, the depressor responses following adrenaline or noradrenaline were constantly greater, in proportion to the degree of intracranial hypertension they induced, than the fall in pressure which followed equal or greater degrees of mechanically induced hypertension (table 5).

Effects of Blockade of Autonomic Ganglions and Partial Section of the Spinal Cord. Injection of tetraethylammonium chloride (TEAC) (15 mg. per Kg. of body weight) into the body of the recipient animal completely abolished the

depressor effects of adrenaline and noradrenaline circulating through the animal's head. The blood pressure of the body fell as a result of tetraethylammonium chloride, much as it does in an intact animal (fig. 5). However, it is important to note that tetraethylammonium chloride did not reduce the blood pressure to as low levels as were previously attained by the central action of adrenaline in the same animal. Further, vasomotor tone of central origin was eliminated by permitting the head of the animal to die by discontinuing perfusion. If the body was kept alive by artificial respiration, blood pressure in the body was 20 to 30

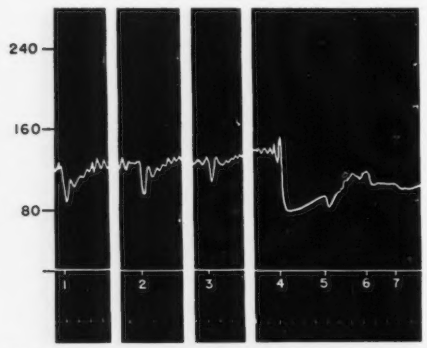

FIG. 5. Effects of tetraethylammonium chloride (TEAC) given to body of recipient dog upon adrenaline induced hypotensive response. *1.* 0.01 mg. adrenaline. *2.* 0.01 mg. adrenaline. *3.* 0.01 mg. noradrenaline. *4.* TEAC, 10 mg. per Kg. to body of recipient. *5.* 0.01 mg. adrenaline. *6.* TEAC, 5 mg. per Kg. *7.* 0.01 mg. adrenaline.

mm. Hg greater than the levels which previously had been noted after injection of adrenaline or noradrenaline.

The spinal cords of 6 animals were progressively, transversely cut with a razor blade while the depressor effects of adrenaline injected into the recipient's cerebral circulation were being observed. The response was not changed until the final sixth of the cord was cut. Histologic study of these cords demonstrated that the fibers which presumably effect the vasodilatation were located in the most peripheral portions of the anterolateral columns. This area has been shown by Wang and Ranson[17] to be the pathway of the sympathetic nervous system.

Effects of Surgical Sympathectomy. Seven animals were subjected to four-stage sympathectomy during which paravertebral ganglions and sympathetic chains were removed bilaterally from the stellate to the fourth lumbar ganglions. After six to eight weeks' recovery, these dogs were used as recipients in perfusion experiments. During the preparation the carotid sinuses were denervated and the vagus nerves were sectioned. None of these animals exhibited a fall in blood pressure regardless of the amount of adrenaline injected into the arterial circulation of the isolated head. Dosages as high as 0.1 mg. of adrenaline were without peripheral effect.

The Effects of Blocking Agents on the Vasodepressor Response of Centrally Acting Adrenaline and Noradrenaline. Blocking agents were given in an attempt to define the nature of the vasodepressor response induced in the recipient dog's body by centrally acting adrenaline or noradrenaline. *Atropine sulfate* (2.6 mg.) was given by vein to both the donor and recipient animals so that the depressor effect of intravenously injected Mecholyl (acetyl-β-methylcholine) (0.5 mg.) was abolished. This did not alter the depressor response of the recipient's body to the injection of adrenaline or noradrenaline into the cerebral circulation.

Benzodioxane was given to the recipient's body (as much as 5 mg. per Kg. of body weight). This was without effect upon the depressor response. However, this adrenolytic drug inhibits only the pressor effects of adrenaline and noradrenaline; hence this evidence does not exclude the possibility that the effector agent responsible for peripheral dilatation was an adrenaline-like substance with only vasodepressor qualities, such as Isuprel [1(3′,4′-dihydroxyphenyl)-2-isopropylaminoethanol].

Ergotamine tartrate at times will convert the depressor effects of Isuprel to pressor. In 4 experiments ergotamine tartrate was given to the recipient dog's body in amounts as great as 5 mg. After ergotamine, intravenously injected Isuprel caused some initial pressor response; its action, however, continued to be predominantly depressor. Further, the depressor effects of centrally acting adrenaline and noradrenaline were unchanged.

Benadryl was given to the recipient dog until intravenous injection of 0.1 mg. of histamine phosphate caused no reduction of blood pressure. But it did not inhibit the depressor phenomenon under study.

Effects of Inhalation of Carbon Dioxide by Donor Dog. In 6 experiments the donor dogs were given mixtures of 5 to 70 per cent carbon dioxide and 30 to 95 per cent oxygen by respirator, after paralyzing doses of curare were given to prevent struggling and hyperpnea in response to the carbon dioxide. With concentrations 40, 50, 60 and 70 per cent, there was lowering of the donor dog's blood pressure. The recipient dog showed no change even when the *p*H of the donor blood was as low as 6.5. The recipient animals exhibited hyperpnea in response to carbon dioxide brought by the blood of the donor animal and usually it was necessary to curarize them to prevent excessive respiratory combat.

In 5 experiments the recipient animals' bodies were given carbon dioxide and oxygen by respirator. Unless the concentration of carbon dioxide exceeded 40 per cent there was no change in blood pressure. With the higher concentrations the blood pressure was lowered by 40 to 50 mm. Hg from the control levels of 120 to 150.

Effects of Intravenous Injections of Adrenaline and Noradrenaline in the Decapitated Animal. In 4 experiments animals were decapitated and the body maintained alive by artificial respiration. Intravenous injections of adrenaline caused the usual rise and subsequent depressor phase commonly noted in intact animals. Noradrenaline was always pressor. After injection of tetraethylammonium chloride the pressor responses were augmented as in an intact animal. If the pressor effects of adrenaline or noradrenaline were inhibited by previous injection of Priscoline (3 to 5 mg. per Kg. of body weight) adrenaline was entirely vasodepressor while noradrenaline was almost without effect upon the blood pressure.

Peripheral Hemodynamic Changes Induced by Centrally Acting Adrenaline. Doctors J. W. Remington and W. F. Hamilton were kind enough to estimate the changes in cardiac output and peripheral resistance which occurred during the hypotensive state induced by centrally acting adrenaline. Calculation of these values was made from optical records of the carotid pulse wave.[18] Records were made by Mr. F. Olmsted.

During adrenaline-induced hypotension there was little change in pulse rate, cardiac output was increased from 1.14 to 1.88 liters per minute and the ratio indicative of peripheral resistance reduced from 5.9 to 2.3 (table 6).

TABLE 6.—*Peripheral Hemodynamic Changes Induced by Centrally Acting Adrenaline*

	Arterial B.P.	Pulse Rate	Cardiac Index	Index of Peripheral Resistance
	mm. Hg		*L./min.*	
Control	142/123	154	1.14	5.9
After Adrenaline	99/85	146	1.88	2.3

DISCUSSION

These experiments demonstrate that adrenaline and noradrenaline acting solely on the central nervous system cause sudden sharp reduction of the peripheral blood pressure.

This vasodepressor effect occurs whether or not the carotid bodies, carotid sinuses, aortic depressor, or vagus nerves are present. When the carotid sinuses are functioning the degree of blood pressure fall which can be produced by distention of the carotid sinus by rapid injection of 25 cc. of normal saline into the carotid artery is not nearly as great as when 0.01 mg. of adrenaline in a similar volume of saline is so injected (12 to 20 as compared with 30 to 40 mm. Hg). Further, if the blood pressure in the isolated dog's head with intact carotid sinuses is elevated equally, first with adrenaline and then with a pump, the fall in blood pressure of the recipient body which follows the mechanical elevation of perfusing pressure is about 40 per cent less than that produced by adrenaline.

If the carotid sinuses are denervated, changing the perfusion pressure by eliciting hypotension from bleeding of the donor dog, or elevating its pressure by intra-arterial transfusion of blood under pressure, does not change the blood pressure of the body of the recipient.

Further, altering the perfusing pressure by use of a pump so that the blood pressure curve of intracranial pressure, as recorded from the clamped carotid artery, resembles that produced by intra-arterial injection of adrenaline causes no change of pressure in the body of the recipient dog. These results differ from those of Nowak and Samaan[15] who found a fall of blood pressure in the body of recipient dogs similarly studied. They depended, however, upon sectioning of the nerve of Hering as it arose from the carotid bifurcation to denervate the sinuses. Also they do not mention testing for carotid sinus activity before initiating their experiments. Since Code, Dingle and Moorhouse[19] have demonstrated that nerve fibers can enter the nerve from the carotid sinus until it enters the jugular foramen, it seems possible the carotid sinuses of the dogs used by Nowak and Samaan were still functioning.

That the impulses which produce hypotension in the recipient as the result of perfusing pressor agents in the brain are mediated through the sympathetic nervous system is likely since (1) progressive transection of the cord showed the pathways involved to be in the peripheral aspect of the anterolateral columns, and (2) pharmacologic ganglionic blockade by tetraethylammonium chloride, surgical ganglionectomy and lumbodorsal sympathectomy abolished the response to centrally acting adrenaline and noradrenaline.

Since adrenaline and noradrenaline have no effect on peripheral arterial pressure when introduced into the fluid of the lateral ventricles or into the cisterna magna, it is reasonable to assume that impulses for peripheral vasodilatation arise from centers which are in some manner affected by the vasoconstrictor drugs in the blood circulating through them. These centers might be influenced by the rate of their perfusion as determined by local vasoconstriction or vasodilatation. Also, the drugs might have a direct action upon nerve cells. If the former explanation is correct, there must be adequate evidence that adrenaline constricts intracranial vessels, particularly those of the medulla. Support for this view is furnished by the work of Forbes and Wolff[20] and Bouckaert and Jordan.[21] The former showed that injection of adrenaline into the carotid artery, application of it to the pia-arachnoid or stimulation of the cervical sympathetic nerves caused reduction of almost 10 per cent in the caliber of the pial vessels. Bouchaert and Jordan isolated the intracranial from the extracranial circulation by ligation of all visible extracranial vessels, detached the head from the body and found elevation of intracranial arterial blood pressure after injection of adrenaline into the perfusing circuit.

Schmidt[22] demonstrated the presence of vasoconstrictor innervation through the cervical sympathetics by means of a thermocouple in the hypothalamic and parietal areas of cats. Adrenaline and sympathetic stimulation caused no reduction of blood flow through the medulla which is the region believed to contain the vasoconstrictor centers.[23] The only substance which significantly influenced the flow through this vascular bed was inspiration of carbon dioxide which produced easily measurable vasodilatation.

If the peripheral depressor response to adrenaline and noradrenaline was due to local vasoconstriction in the medulla, and the hypertension which follows circulation of Mecholyl and histamine through the brain resulted from local vasodilatation[24] it would be expected that the potent vasodilator, carbon dioxide, would cause a rise of pressure in the body of the recipient dog. This was not the case. Hence, we ascribe the central action of drugs to action upon chemoreceptors, the location of which is not known.

The hypotension which follows the cerebral action of adrenaline is, then, the result of peripheral vasodilatation and decreased peripheral resistance. Since this effect is not abolished by atropine or Benadryl in the recipient animal's body, it is unlikely that it occurs because of the release of acetylcholine or histamine at nerve endings. Although benzodioxane and ergotamine in amounts sufficient to reverse adrenaline or inhibit noradrenaline do not alter the response, this does not exclude the possibility that an adrenaline-like substance is released at the sympathetic nerve endings, since

Isuprel continued to be vasodepressor when given to dogs that had received these blocking agents.

Another possible explanation of the hypotensive action of adrenaline or noradrenaline is central blockade of the vasomotor areas and consequent loss of vasomotor tone in the periphery. Against this is the fact that tetraethylammonium chloride, in doses known to cause autonomic ganglionic blockade and thus remove vasomotor tone of central origin, did not reduce the blood pressure of recipient dogs to as low a level as was previously observed following action of adrenaline and noradrenaline. Further, when the brain was permitted to die from anemia and central vasomotor tone was no longer a factor, the blood pressure did not fall to the levels elicited by adrenaline and noradrenaline. Thus since the hypotension is not merely a release of tone, we believe that adrenaline and noradrenaline, through central action, stimulate the sympathetic nervous system to produce active vasodilatation. The observation that vasodilatation may be induced by stimulation of the sympathetic nervous system is not new.[25–27]

The quantitative relationship of centrally induced peripheral vasodilatation to the peripheral vasoconstrictor effects of adrenaline and noradrenaline in the intact animal is not known. Central action is not the sole cause of the depressor phase of adrenaline action, since noradrenaline and adrenaline are both constantly vasodepressor when acting centrally, and yet, in intact animals, noradrenaline rarely induces a fall in blood pressure. Furthermore, we have shown that in the bodies of decapitated dogs, when the pressor action of adrenaline is inhibited by Priscoline, the vasodilator effect of adrenaline persists as in intact animals.

The demonstration that fall in blood pressure regularly follows the perfusion of the brain with pressor agents and rise follows depressor agents, and that the fall and rise are independent of the carotid sinus mechanism and the perfusing pressure, indicates that a chemoreceptor system exists within the brain. Although the location of the receptors is not known, the outflow is over the sympathetic nervous system.

The pressor action of a drug is thus modified by centrally induced peripheral vasodilatation and the vasodepressor effect of dilator drugs is buffered by centrally induced peripheral vasoconstriction. Abolishing the action of this central buffer mechanism by sympathectomy, spinal cord section at C-6, or tetraethylammonium chloride administration along with loss of the carotid sinus buffers, explains in part, we believe, the greatly augmented response to vasoactive drugs.[28]

Baroreceptors apparently do not occur within the blood vessels of the brain, because we were unable to change peripheral arterial pressure by elevating the pressure of the blood perfusing the dog's brain with a pump. Pressures as high as those produced by injecting adrenaline into the donor animal produced no change while the adrenaline elicited a sharp fall in pressure. The baroreceptors responsive to changes in cerebrospinal fluid pressure we shall consider in a separate communication.

Alteration or loss of the ability of the cerebral buffer system to respond by peripheral dilatation to pressor substances manifestly might be a mechanism responsible for the development of essential hypertension.

Summary

1. A method has been described for perfusion of a dog's brain connected to its body only by the nervous system; by this method no blood leaks into the body.

2. In 127 experiments it was shown that adrenaline and noradrenaline injected into the perfusion circuit constantly reduced the blood pressure of the recipient's body, roughly in proportion to the amount of pressor agent administered. The depressor response was largely independent of the pressor response of the donor. Neither drug causes this effect when injected into the cerebrospinal fluid.

3. Depressor substances such as histamine and acetylcholine when perfused through the brain caused a marked rise in the recipient's blood pressure.

4. These effects could be produced inde-

pendently of the carotid sinus buffer mechanism. Mechanical elevation or lowering of the perfusion pressure within the brain failed to alter the arterial pressure of the recipient's body, although pressures were attained comparable to those after injection of pressor and depressor substances.

5. Lumbodorsal sympathectomy, selective section of the spinal cord, and autonomic ganglionic blockade by tetraethylammonium chloride all abolished the central response to adrenaline and noradrenaline. Atropine, benzodioxane, ergotamine, and Benadryl given to the recipient's body all failed to block the central depressor responses. Carbon dioxide lowered the arterial pressure in the curarized donor dog but did not affect the pressure of the recipient's body. When the carbon dioxide was given to the recipient's body, arterial pressure fell.

6. In decapitated animals adrenaline was both pressor and depressor and noradrenaline only pressor. Both were augmented by tetraethylammonium chloride, but after Priscoline adrenaline was depressor and noradrenaline almost inactive.

7. Estimation of cardiac output from pressure pulse tracings showed, after centrally induced adrenaline hypotension, an increase and reduction of peripheral resistance.

Conclusions

By means of a special technic for perfusing the brain of a dog joined to its body only by the nervous system, chemoreceptors have been found in the brain. These respond to adrenaline and noradrenaline by lowering arterial pressure sharply and to histamine and acetyl-β-methylcholine by raising it. Baroreceptors were not found within the vessels. This cerebral buffer system is probably of importance in determining the response to humoral vasoactive substances, hence in the mechanism of hypertension and shock.

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The Effect of Cycle Length on the Time of Occurrence of the First Heart Sound and the Opening Snap in Mitral Stenosis

By ADDISON L. MESSER, M.D., TIMOTHY B. COUNIHAN, M.D., MAURICE B. RAPPAPORT, E.E. AND HOWARD B. SPRAGUE, M.D.

Phonocardiography is often more valuable than electrocardiography in timing mechanical events in the cardiac cycle. This study shows that the opening and closing of the mitral valve are related to the length of the previous heart cycle as demonstrated by the variations occuring in auricular fibrillation. These variations in valve action are controlled by the pressure gradient between left auricle and ventricle.

THE vibrations of the heart sounds are an immediate manifestation of various mechanical activities of the heart, and, when suitably recorded, provide an excellent way of timing events which comprise the cardiac cycle. It is important, therefore, to recognize the effect of disease on the time of occurrence of these vibrations, their probable mode of production, and their relationship to other events in the cardiac cycle.

It is agreed by most observers that the beginning of electrical activity in the heart muscle precedes mechanical activity as manifested by the vibrations of the first heart sound [1a, b, c]; however, this discrepancy between mechanical and electrical events is more apparent than real. The spread of electrical activity in the myocardium occurs with extreme rapidity and, while mechanical contraction probably begins almost simultaneously,[2] a short interval of time is required to produce a significant shortening of the muscle fibers. During this initial phase of ventricular systole, a few low intensity, low frequency vibrations occur (first component of the first heart sound[3]). These are followed by a group of large amplitude vibrations (second and third components), which comprise the main vibrations of the first heart sound. The beginning of these latter vibrations is generally accepted as being due to atrioventricular valve closure[4] and time this event rather precisely. It is these large amplitude vibrations of the first heart sound, and therefore atrioventricular valve closure, which follow the beginning of electrical activity by an appreciable interval. The initial low frequency, low amplitude vibrations, which precede atrioventricular valve closure, may not be recorded if the technic is incorrect, or may be obscured by a diastolic murmur occurring during the presystolic interval. They occur, however, whether normal rhythm or auricular fibrillation is present.[3]

Luisada[5] has recently pointed out that the interval between the beginning of the upstroke of the electrocardiographic R wave and the main vibrations of a simultaneously registered first heart sound may not be a constant one. The reason for this variation has not been adequately elucidated; however, it is apparent that a delay in atrioventricular valve closure would increase this interval.

Opening of the atrioventricular valves results in certain vibrations related to the second heart sound (fourth component).[6] These vibrations are frequently audible in mitral stenosis and are easily identified on an adequately recorded phonocardiogram. Margolies and Wolferth[7] found that in patients with auricular fibrillation and mitral stenosis the time of occurrence of this sound (designated as the "opening snap" of the mitral valve) in relation to the beginning of the second heart sound varied with the pre-

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ceding diastolic interval, tending to become shorter as the preceding cycle duration decreased.

In a recent analysis of 55 cases of mitral stenosis[8] it was found that many of these cases showed a delay in the beginning of the main vibrations of the first heart sound with regard to the beginning of the upstroke of the R wave of a simultaneously recorded electrocardiogram. This indicated a delay in closure of the mitral valve and suggested two possible explanations: (1) that stiffening of the mitral leaflets rendering them less pliable might slow their movement or closure, or (2) that an increase in left atrial pressure might appreciably delay the mitral valve closure, since left ventricular pressure must exceed that in the left atrium in order to effect valvular closure.

The following study was undertaken in order to determine if the variations noted by us and others were chance variations or were significantly related to changes in the cardiac cycle affecting left atrial pressure. Patients with auricular fibrillation and high grade mitral stenosis were selected in order to exclude the effect of atrial contraction on intra-atrial pressure at the beginning of ventricular systole and to obtain frequent variations in cycle length.

Method of Study and Results

Six sets of phonocardiograms were taken on 5 patients with auricular fibrillation and well-developed mitral stenosis; on one of the 5 patients, the records were retaken two years later (cases 64 and 338). Limb lead II of the electrocardiogram was recorded simultaneously as a reference tracing; although we realize a part of the QRS complex may be isoelectric in this lead, the error would be a constant one and would not affect the calculations in this study. The time between the beginning of upstroke of the R wave of the electrocardiogram and the beginning of the main vibrations of the simultaneously registered first heart sound was measured and correlated with the length of the preceding R-R interval of the electrocardiogram. The time between the beginning of the main vibration of the second heart sound and the beginning of the opening snap of the mitral valve was measured and correlated in a similar fashion with the preceding R-R interval of the electrocardiogram.

The results, with the coefficients of correlation for both variables and their standard error, are shown in table 1. It is apparent from these figures that a significant degree of correlation exists between the preceding cycle length as measured by the R-R interval of the electrocardiogram and the beginning of the R wave–first sound interval as well as the second sound–opening snap interval. For the purpose of this study a linear correlation was assumed; although it is probable that at the extremes of cycle length both variables approach maximum and minimum values beyond which no variation occurs.

Table 1.—*The Degree of Correlation Which Exists between the Preceding Cycle Length as Measured by the R-R Interval of the Electrocardiogram and the Beginning of the R Wave-First Sound Interval as well as the Second Sound-Opening Snap Interval*

Case Number	Number of Observations	Coefficients of Correlation		Standard Error
		QRS-First Sound	Second Sound-Opening Snap	
64	20	−0.7	0.7	0.229
282	43	−0.6	0.85	0.154
295	32	−0.6	0.8	0.179
302	43	−0.3	0.6	0.154
303	37	−0.7	0.7	0.166
338	22	−0.7	0.8	0.218

When the preceding cycle length is short the vibrations of the first sound are delayed with respect to the beginning of electrical activity and, as the preceding cycle length increases, the beginning of the R wave–first sound interval decreases. When the preceding cycle length is short, the second sound–opening snap interval is short and as the cycle length increases, the second sound–opening snap interval increases. Figure 1 illustrates these findings.

Additional evidence of the importance of left atrial pressure is provided by the following observations on the duration of the mitral diastolic murmur. When diastole is very long the murmur begins with the opening snap of the

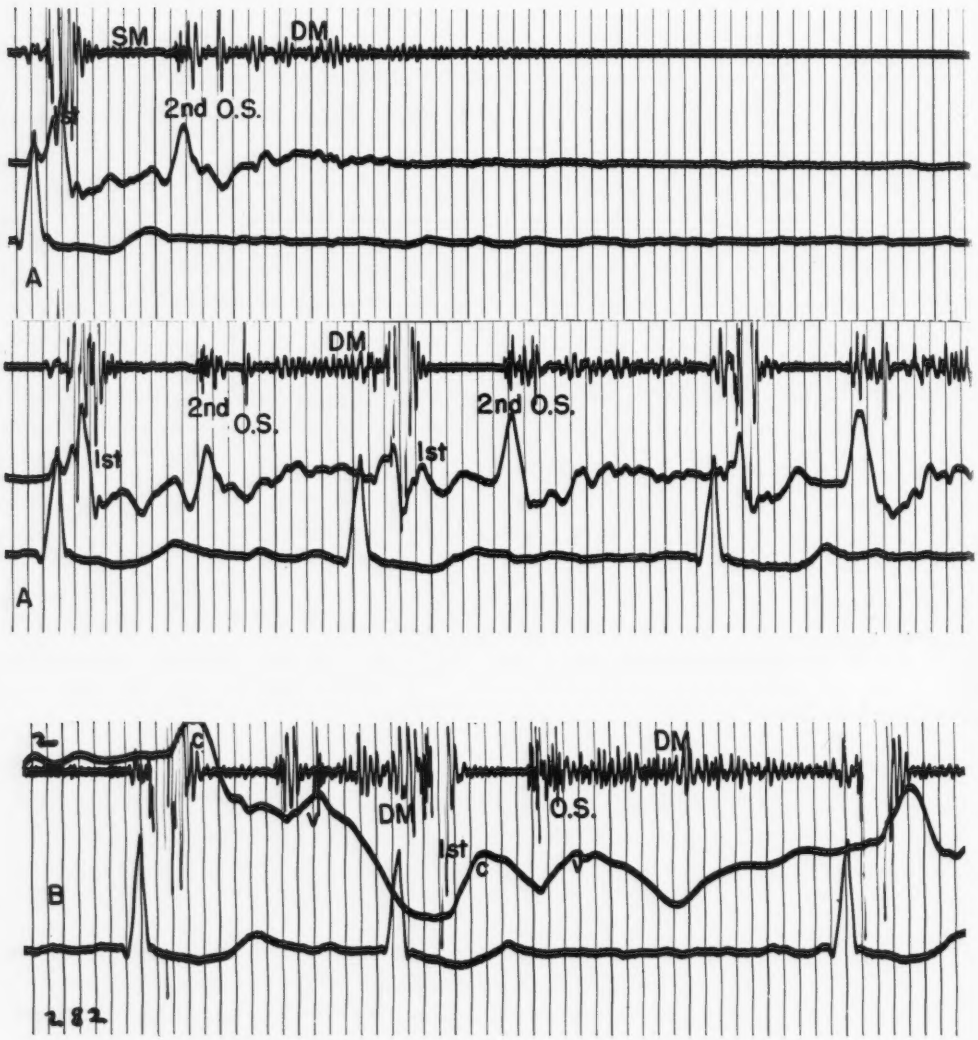

FIG. 1*A*. Continuous apex phonocardiogram, apex cardiogram and electrocardiogram showing the variation of the first heart sound and the opening snap (OS) of the mitral valve with the preceding cycle length. There is a low intensity systolic murmur (SM) and a more intense low frequency diastolic murmur (DM).

B. Phonocardiogram recorded at the apex, venous pulse and electrocardiogram. During the short diastolic interval the diastolic murmur continues after the beginning of electrical activity up to the delayed first heart sound.

mitral valve, reaches its maximum intensity very soon, then gradually decreases in intensity, completely fading out before the first heart sound. If diastole is short, the murmur begins in the same manner; however, since there is not sufficient time for the left atrium to empty before the next systole, the murmur lasts throughout diastole to the very beginning of the first heart sound. Under the latter condition, the murmur is not only presystolic but, since the

beginning of the first sound is delayed, actually extends for a short interval after the beginning of electrical systole (figure 1*B*).

While the correlation between the beginning of electrical activity and the beginning of the first heart sound is an inverse one, the relationship between the beginning of the second sound and the opening snap of the mitral valve is a direct one. When the preceding cycle length is short, the second sound–opening snap interval is short and increases directly with the duration of the preceding cycle length.

Discussion

Luisada,[5] in discussing the influence of cycle length on the time of occurrence of the first heart sound, suggested that "in some cases of auricular fibrillation when diastole is very short, the contraction of the ventricles is slightly delayed. This differing relationship between the electric and acoustic waves seems to point to the possibility of a dissociation between excitation and contraction of the ventricles." Our findings indicate there is no dissociation between electrical excitation and the beginning of mechanical contraction, but rather a delay between the beginning of contraction and the time of closure of the mitral valve. This delay is due to the time required for sufficient muscular tension to develop so that the left intraventricular pressure exceeds that in the left atrium. It is unlikely that stiffening of the mitral leaflets contributes to this delay since there is no delay when the preceding cycle length is great.

Measurements of left atrial pressure in patients with well-developed mitral stenosis have shown this pressure to be markedly elevated.[9] Variations in the length of the cardiac cycle occur mainly at the expense of diastole. When diastole is short, less time is afforded the blood of the left atrium to pass through the narrowed mitral orifice; hence, at the beginning of the subsequent systole, mitral valve closure is not effected until left intraventricular tension exceeds that in the atrium. This is manifested by a delay in the beginning of the main vibrations (second component) of the first heart sound with respect to the beginning of electrical activity. The reverse of this takes place when diastole is long because left atrial emptying is more nearly complete at the beginning of the succeeding ventricular systole. Additional evidence of the importance of left atrial pressure and its relation to diastolic emptying time is shown by the configuration of the mitral diastolic murmur. When diastole is short this murmur continues with undiminished intensity to the beginning of the delayed first heart sound, but fades completely before the occurrence of the first sound when diastole is long.

The opening snap of the mitral valve was found to occur at varying times with regard to the second heart sound by Margolies and Wolferth.[6] They suggested that the effect of the previous cycle length on the atrioventricular pressure gradient was the determining factor. Our finding of a significant correlation between the second sound–opening snap interval and the preceding cycle length confirms this view. Furthermore, the close correlation between this interval and that of the beginning of the upstroke of the electrocardiographic R wave–first sound interval with the preceding cycle length indicates a common mechanism is responsible for both. The second heart sound times precisely the closure of the semilunar valves and occurs when the ventricular pressures fall below that in the pulmonary artery and aorta. The beginning of ventricular diastole (relaxation) follows this event, and the mitral valve opens at the point where ventricular pressure falls below that in the left atrium. Following a short diastolic interval, left atrial pressure remains high during systole and, therefore, the mitral leaflets are forced open earlier during the succeeding diastole. If the preceding cycle length is long, the above factors do not occur and the interval between the second heart sound and the opening sound of the mitral valve increases.

The variations of these two intervals and their close correlation with the preceding cycle length confirm the importance of the atrioventricular pressure gradient as the determining factor. If stiffening of the mitral leaflets played an important role, the preceding diastolic interval should have little or no effect on these intervals. Furthermore we would not expect the beginning of the electrocardiographic R wave–first sound interval to be increased

when in the same cycle the second sound–opening snap interval is *decreased*.

These findings confirm the clinical experience that patients with well-developed mitral stenosis do not tolerate rapid heart rates. When the diastolic interval is long enough for the left atrium to discharge its contents into the left ventricle even high grade mitral stenosis may be well tolerated. Tachycardia due to any cause, emotion, effort, infection, or an abnormal rhythm, is frequently sufficient, in these patients, to produce severe attacks of pulmonary engorgement and edema due to incomplete left atrial emptying.

Summary and Conclusions

1. Phonocardiograms registered simultaneously with the electrocardiogram on patients with auricular fibrillation and mitral stenosis show that the temporal relationships of the sounds produced by the opening and closing action of the mitral valve bear a relationship to the duration of the preceding cardiac cycle. When the preceding cycle length is short, the mitral valve closure is delayed with respect to the commencement of electrical activity (the beginning of the upstroke of the electrocardiographic R wave). Also, the interval between the second heart sound component (closure of the semilunar valves) and the opening snap of the mitral valve is shortened.

2. Evidence is presented which shows that in mitral stenosis the factor which relates preceding cycle length to the time of occurrence of the sounds of mitral valve closure and opening is the atrioventricular pressure gradient between the left heart chambers.

3. Due to the fact that the time intervals between electrical and mechanical cardiac events are variable and dependent upon the preceding cycle length, the usefulness of the electrocardiogram as a reference tracing for the precise timing of mechanical events is limited.

4. A suitably registered phonocardiogram provides a more accurate reference tracing for timing mechanical events in the cardiac cycle than does an electrocardiogram.

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New Aspects of Blood Pressure Regulation

By C. HEYMANS, M.D., AND G. VAN DEN HEUVEL-HEYMANS, M.D.

Experiments show that the state of tone and contraction and thus the resistance to stretch of the arterial wall where the pressoceptors of the carotid sinus are located, are the primary factors affecting these receptors which regulate and moderate reflexly the systemic arterial pressure. Decrease of resistance to stretch of the arterial wall, where the receptors of the sinoaortic nerves which moderate reflexly the general arterial pressure are situated, could be the primary mechanism of essential hypertension.

IT IS known that the cardio-aortic and carotid sinus pressoceptor nerves are not only the means of physiologic blood pressure regulation, but also are the reflex buffer or moderator nerves of the arterial pressure. This reflex regulation of blood pressure occurs by the action of arterial pressure itself on receptors located in the vascular walls of the sino-aortic areas.

Experiments of Koch,[1] Heymans and coworkers[2] and Hauss and associates[3] showed that arterial pressure does not act directly on the receptors of the sino-aortic areas, but indirectly by stretching the wall of the arteries where the sino-aortic receptors are located.

These experimental observations suggested that the state of contraction, tone, elasticity and resistance to stretch of the arterial wall of the sino-aortic areas could play a role in the mechanisms of reflex regulation and homeostasis of arterial pressure.

This suggestion has been investigated in a series of experiments in order to examine the influence on arterial pressure and on the reflex homeostasis of blood pressure, of different drugs affecting the tone and resistance to stretch of the arterial wall of the carotid sinus.

METHODS

Dogs were anesthetized with morphine (1 mg. per Kg. subcutaneously) and chloralosane (100 mg. per Kg. intravenously). The vagi-aortic nerves were cut in order to limit the reflex regulation and homeostasis of blood pressure to the receptors of the carotid sinuses. The systemic blood pressure was registered with a mercury manometer from a femoral artery. The drugs were applied to the wall of the arteries of the carotid sinus by injection of 2 to 4 ml. of the solutions into the external conjunctival space surrounding both carotid sinus areas.

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EXPERIMENTS

It has been shown in a previous group of experiments[4] that local application of *l*-adrenaline hydrochloride, *l*-noradrenaline hydrochloride, diacetyladrenaline thiosulfonic acid,[5] or Pitressin on the carotid sinuses induces a progressive and prolonged fall of the systemic arterial pressure, and decreases or suppresses the hypertensive response provoked normally by the lowering of blood pressure in the carotid sinuses.

These phenomena induced by the local application of adrenaline, noradrenaline or Pitressin on the arterial walls of the carotid sinus are due to a stimulation of the carotid sinus pressoreceptors which moderate reflexly the general arterial pressure. Indeed, section of the carotid sinus nerves, when the arterial pressure has been lowered by local application of the drugs on the carotid sinus areas, provokes an immediate and very marked rise of the systemic arterial pressure.

In another series of experiments,[4] drugs known to relax smooth muscles were applied locally to the wall of the arteries of the carotid sinuses. These experiments showed that local application of a small dose of papaverine or benzylimidazoline (Priscoline) on the carotid sinuses causes a reflex rise of systemic arterial pressure. The vasopressor reflexes of carotid sinus origin are maintained and eventually increased. The local application of these drugs on the carotid sinus areas reduces the stimulation

of the pressoreceptors which moderate reflexly the arterial pressure and consequently induces a rise of systemic blood pressure.

The action on blood pressure of locally applied adrenaline or noradrenaline to the carotid sinus may be reversed by local carotid sinus application of an adrenolytic drug.[6]

These experiments have been extended mainly in order to determine the threshold dose of adrenaline or noradrenaline able to induce a reflex fall of the systemic arterial pressure by their local action on the carotid sinus areas.

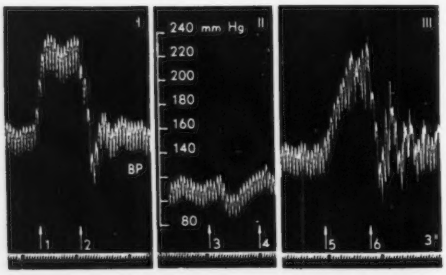

FIG. 1. Dog weighing 16.5 Kg. Blood pressure from femoral artery. ↑1 — ↑2: clamping and unclamping of common carotid arteries. Between I and II: local application of 2.5 μg. adrenaline on carotid sinuses. II: blood pressure 5 minutes after local carotid sinus application of adrenaline. ↑3 — ↑4: clamping and unclamping of common carotid arteries. III: 20 min. after II. ↑5 — ↑6: clamping and declamping of common carotid arteries.

This problem has indeed not only a pharmacologic, but also a biologic importance.

Adrenaline

l-Adrenaline hydrochloride* in isotonic saline solution was used. Clamping (↑1, fig. 1) of the common carotid arteries (hypotension in carotid sinuses) induces, under normal conditions, a marked reflex rise of the systemic arterial pressure. Unclamping (↑2, fig. 1) of the carotid arteries (rise of pressure in carotid sinuses) provokes a return to normal systemic arterial pressure.

Local application of 2.5 μg. of adrenaline on each carotid sinus area induces a progressive fall of the systemic arterial pressure (II, fig. 1) and suppresses the hypertensive response (↑3–↑4, fig. 1) provoked normally by the decrease of pressure in the carotid sinuses. The systemic arterial pressure returns progressively to normal levels (III, fig. 1) and the hypertensive response induced by clamping both carotid arteries also returns to normal values (↑5–↑6, fig. 1), about 20 minutes after carotid sinus application of the small amount of adrenaline.

Local application on the carotid sinus areas of higher doses of adrenaline provokes the same, but still more prolonged, reflex fall of the systemic arterial pressure and a suppression of the normally induced reflex hypertensive response caused by the decrease of pressure in the carotid sinus.

Noradrenaline

l-Noradrenaline hydrochloride in isotonic saline solution was used. Clamping (↑1, fig. 2) of the common carotid arteries (hypotension in carotid sinuses) provokes, under normal conditions, a marked reflex rise of the systemic arterial pressure. Unclamping of the carotid arteries (↑2, fig. 2) induces a reflex return to normal systemic arterial pressure.

Local application of 10 μg. noradrenaline on each carotid sinus area causes only a slight fall of the systemic arterial pressure (II, fig. 2), but induces a marked decrease of the carotid sinus hypertensive reflexes (↑3–↑4, fig. 2). About 30 minutes after the local carotid sinus application of noradrenaline, the carotid sinus hypertensive reflexes are again normal (↑5–↑6, fig. 2). Clamping (↑1, fig. 3) and unclamping (↑2, fig. 3) of the common carotid arteries induce the normal reflexes on the systemic arterial pressure. Local application of 200 μg. noradrenaline on each carotid sinus area provokes a marked reflex fall of systemic arterial pressure (II, fig. 3) and a suppression of the carotid sinus reflexes (↑3–↑4, fig. 3). About 43 minutes later, the arterial pressure is still low (III, fig. 3) and the carotid sinus hypertensive reflexes are practically absent (↑5–↑6, fig. 3). Section (↑7, fig. 3) of both carotid sinus nerves provokes an immediate and very marked rise of the systemic arterial

* Pure *l*-adrenaline and *l*-noradrenaline have kindly been supplied by the Sterling-Winthrop Research Institute.

pressure from 80 to 300 mm. Hg. This fact shows again that the local application of noradrenaline on the carotid sinus areas induces a fall of the systemic arterial pressure by increase of the reflex moderating action of the

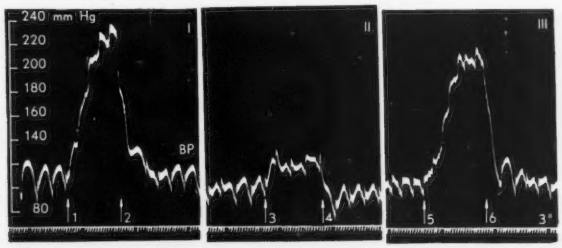

FIG. 2. Dog weighing 15 Kg. Blood pressure from femoral artery. ↑1 – ↑2: clamping and unclamping of common carotid arteries. Between I and II: local application of 10 μg. noradrenaline on carotid sinuses. II: 10 minutes after local carotid sinus application of noradrenaline. ↑3 – ↑4: clamping and unclamping of common carotid arteries. III: 30 min. after II. ↑5 – ↑6: clamping and unclamping of common carotid arteries.

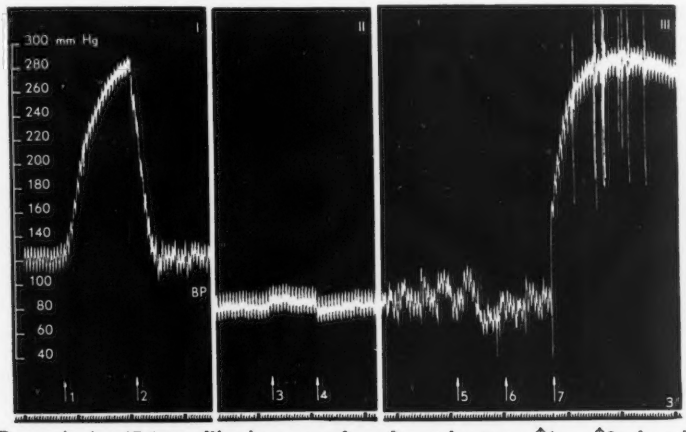

FIG. 3. Dog weigaing 17.5 Kg. Blood pressure from femoral artery. ↑1 – ↑2: clamping and unclamping of common carotid arteries. Between I and II: local application of 200 μg. noradrenaline on carotid sinuses. II: about 10 minutes after I. ↑3 – ↑4: clamping and unclamping of common carotid arteries. III: about 45 minutes after II. ↑5 – ↑6: clamping and unclamping of common carotid arteries. ↑7: section of both carotid sinus nerves.

carotid sinus receptors and nerves on the arterial pressure.

Potassium Chloride

Clamping (↑1, fig. 4) and unclamping (↑2, fig. 4) of the common carotid arteries induce the normal reflexes on the systemic arterial pressure.

Local application (↑3, fig. 4) of 40 mg. potassium chloride in 0.4 ml. of water on the carotid sinus areas provokes a marked rise of the systemic arterial pressure (II, fig. 4). The carotid sinus reflexes on the arterial pressure are not only maintained, but still more pronounced (↑4–↑5, fig. 5). About 16 minutes after the local carotid sinus application of potassium chloride, the systemic arterial pressure and the carotid sinus reflexes (↑6–↑7, fig. 4) are again normal.

Smaller amounts of 2 to 10 mg. potassium chloride applied to the carotid sinus areas induce similar reactions of reflex rise in systemic arterial pressure.

Dibenamine

As already shown,[6] after local application of the adrenolytic compound, *N*-(2-bromo-

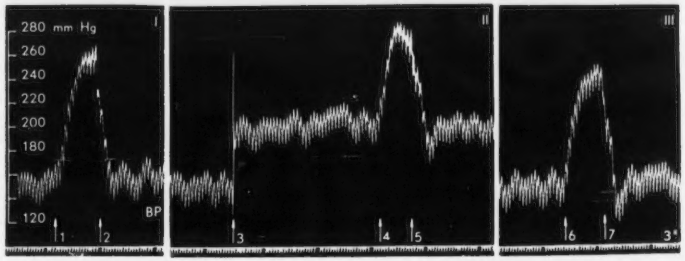

FIGURE 4

FIG. 4. Dog weighing 25 Kg. Blood pressure from femoral artery. ↑1 — ↑2: clamping and unclamping of common carotid arteries. ↑3: local application of 40 mg. potassium chloride on carotid sinuses. ↑4 — ↑5: clamping and unclamping of common carotid arteries. III: about 16 minutes after II. ↑6 — ↑7: clamping and unclamping of common carotid arteries.

FIG. 5. Dog weighing 26 Kg. Blood pressure from femoral artery. ↑1 — ↑2: clamping and unclamping of common carotid arteries. ↑3: local application of 250 μg. noradrenaline on carotid sinuses. ↑4 — ↑5: clamping and unclamping of common carotid arteries. ↑6: local application of Dibenamine on carotid sinuses. III: about 15 minutes after II. ↑7 — ↑8: clamping and unclamping of common carotid arteries. ↑9: section of both carotid sinus nerves.

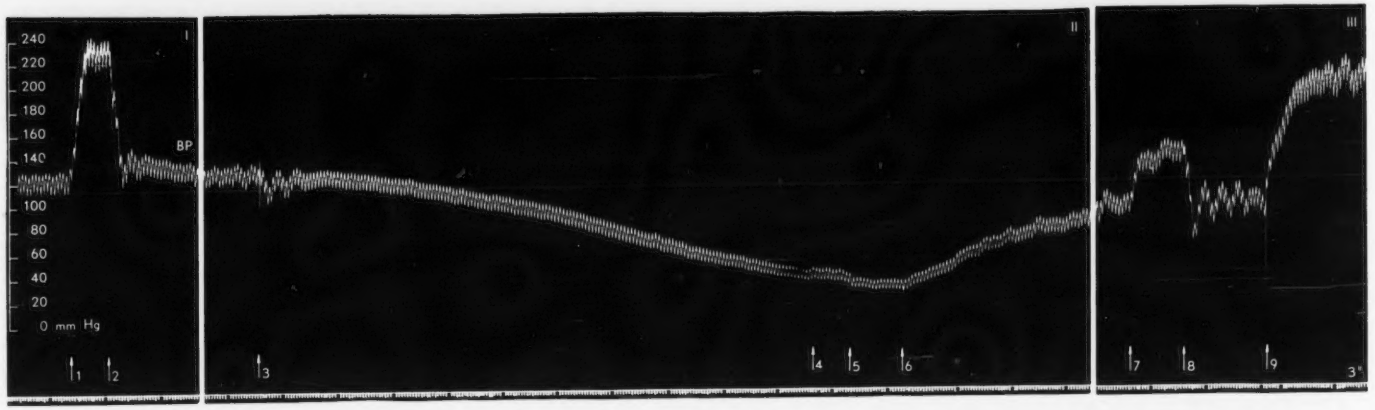

FIGURE 5

ethyl)-*N*-ethyl-*l*-naphthalene methylamine hydrobromide or SY-28, the local application on the carotid sinuses of *l*-adrenaline or *l*-noradrenaline does no more induce a reflex fall, but on the contrary produces a reflex rise of the systemic arterial pressure.

These experiments have been extended to Dibenamine, another adrenolytic drug.

Clamping (↑1, fig. 5) and unclamping (↑2, fig. 5) of the common carotid arteries induce the normal carotid sinus reflexes on the arterial pressure.

Local application (↑3, fig. 5) to the carotid sinus areas of 250 μg. noradrenaline provokes a progressive and very marked reflex fall of arterial pressure. Clamping (↑4, fig. 5) and unclamping (↑5, fig. 5) of the carotid arteries elicit no more changes in arterial pressure.

Local application (↑6, fig. 5) on the carotid sinuses of 2.5 ml. Dibenamine, 1 per cent, provokes a progressive return of blood pressure to normal levels and restores the carotid sinus reflexes (↑7–↑8, fig. 5). Section (↑9, fig. 5) of both carotid sinus nerves induces a marked rise of arterial pressure.

Similar observations were made with adrenaline.

Local application of dihydroergotamine* on the carotid sinus areas also reverses the effects of locally applied adrenaline and noradrenaline.

Discussion

These experiments show that drugs such as adrenaline, noradrenaline and Pitressin, which are known[7, 8] to induce a contraction of the arterial wall, applied to the carotid sinus areas, cause a stimulation of the receptors of the carotid sinus nerves which moderate reflexly the systemic arterial pressure. This stimulation of the carotid sinus pressoceptors induces reflexly a fall of the systemic arterial pressure and decreases or suppresses the hypertensive reflexes normally provoked by decrease of blood pressure in the carotid sinus.

These influences on systemic blood pressure and carotid sinus reflexes of adrenaline and noradrenaline applied locally to the carotid sinus areas are decreased, suppressed or reversed by local application on the carotid sinuses of an adrenolytic drug.

Papaverine, Priscoline and potassium chloride, applied to the arterial wall of the carotid sinus areas, provoke the opposite reactions which are characterized by a reflex rise of the systemic arterial pressure and an increase of the carotid sinus hypertensive reflexes.

These experimental observations thus demonstrate that the state of contraction and the resistance to stretch of the arterial wall where the receptors of the regulator and moderator nerves of blood pressure are located are the primary factors affecting these receptors.

These experiments also show that not increase[9] but decrease of tone and resistance to stretch of the wall of the arteries where the receptors of the moderator nerves of blood pressure are located could be the primary mechanism of essential hypertension.

As the experimental observations show that very small amounts of adrenaline or noradrenaline applied to the carotid sinus areas are effective, and as it has been shown[10–13] that the walls of arteries contain considerable amounts of adrenaline and noradrenaline, it may be suggested that these biologic substances play a role in the maintainance and regulation of the intrinsic tone and resistance to stretch of the arteries where the pressoceptors are located, and thus have a part in the mechanisms of the reflex homeostasis of blood pressure.

Summary

1. Small amounts of adrenaline or noradrenaline applied to the arterial wall of the carotid sinus areas induce a stimulation of the pressoceptors and thus a marked and prolonged reflex fall of the systemic arterial pressure and a decrease or suppression of the hypertensive reflexes normally provoked by a decrease of pressure inside of the carotid sinus.

2. Section of the carotid sinus nerves when the systemic arterial pressure has been lowered by the local application of adrenaline or noradrenaline on the carotid sinus areas causes an immediate and very marked rise of the systemic arterial pressure.

3. Local application on the carotid sinus of the adrenolytic drugs Dibenamine or dihydroer-

* Dihydroergotamine has been kindly supplied by Sandoz Laboratories (Basel).

gotamine suppresses and reverses the effects of locally applied adrenaline and noradrenaline to the carotid sinus areas.

4. Potassium chloride applied to the carotid sinus areas induces a reflex rise of systemic arterial pressure and an increase of the hypertensive carotid sinus reflexes.

5. These experiments show that the state of contraction and thus the resistance to stretch of the arterial wall where the pressoceptors are located are the primary factors affecting these receptors which regulate and moderate reflexly the systemic arterial pressure.

6. The physiologic and pathologic significance of these experimental observations are discussed.

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Experimental Production of Diffuse Proliferative Glomerulonephritis Utilizing Arteriovenous Fistula Stress with Bacteremia

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By combining the effects of systemic cardiovascular stress produced by large arteriovenous fistulas with bacteremia, a new method has been found by which acute diffuse proliferative glomerulonephritis may be produced experimentally.

THE observation has been reported from this laboratory[1, 2] that dogs with large arteriovenous fistula loads spontaneously acquired endocarditis and that some also developed acute diffuse proliferative glomerulonephritis, in the period of six weeks to five months following the construction of their arteriovenous shunts. On the basis of these initial observations, an experimental method has been developed[3, 4] for the production of endocarditis and diffuse proliferative glomerulonephritis in dogs. This method utilizes the cardiovascular stress of bilateral arteriovenous fistulas in the lower extremities plus a bacteremia produced by intravenous injections of relatively small numbers of bacteria. By use of this method, the incidence of endocarditis has been increased to 100 per cent. Proliferative glomerulonephritis has been observed to occur in approximately one-third of these animals with large arteriovenous fistula loads and with endocarditis occurring either spontaneously or induced by bacterial injection. The pathogenesis of the endocarditis and of the glomerulonephritis in these animals is believed to depend upon the fact that a cardiovascular stress such as large arteriovenous fistulas causes certain physiologic alterations to occur within these dogs which result in a significant and specific increase in the susceptibility of the endothelial surfaces of the heart and kidneys to bacteria or to the products of bacterial infection. Moreover, the relatively small numbers of bacteria necessary to produce these lesions in the presence of large arteriovenous fistulas serves further to emphasize this profound effect of a systemic stress in promoting endothelial susceptibility. Thus, it would appear that systemic stress also plays an important role both in the localization and in the development of endocarditis and glomerulonephritis.

It is the purpose of this report to describe the occurrence and pathology of these glomerular lesions in greater detail. We believe that these observations are of significance, since they present a new method and a new approach for reproducing in the kidneys of a readily available experimental animal, such as the dog, a disease the pathogenesis of which in the human is still controversial and a disease the treatment of which is still largely nonspecific.

Plan of Experiments

Below are listed six groups of dogs which have been used in these experiments. The incidence of glomerulonephritis in each of these groups has been determined by microscopic study of kidney sections made from each of the 81 animals. Although the incidence of glomerulonephritis is the primary subject of this report,

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the occurrence of endocarditis in these same animals has been noted for completeness. A more detailed report upon the pathogenesis of endocarditis has been published previously.[4] The six groups of animals included in this study of the incidence of glomerulonephritis are as follows:

Group 1. Twelve Dogs with Large Arteriovenous Fistula Loads Developing "Spontaneous" Endocarditis.

Group 2. Eleven Dogs with Large Arteriovenous Fistula Loads Receiving Intravenous Injections of Beta Hemolytic Streptococci. (Group D, "Strain I.F.")

Group 3. Eight Dogs with Large Arteriovenous Fistula Loads subdivided into: (a) Six Dogs Receiving Intravenous Injections of an Alpha Hemolytic Streptococcus. (b) Two Dogs Receiving a Coagulase Negative Staphylococcus.

Group 4. Four Dogs with Small Arteriovenous Fistula Loads Receiving Intravenous Injections of Beta Hemolytic Streptocci. (Group D, "Strain I.F.")

Group 5. Ten Normal Dogs (Controls) Receiving Intravenous Injections of the Same Bacteria Used in the Experiments of Groups 2, 3, and 4.

Group 6. Thirty-six Dogs from the Same Animal Colony Which Have Been Used in a Wide Variety of Other Experiments.

Bacteriologic Data

In the animals of group 1, all but a few of the earliest dogs studied had repeated blood culture studies done. The organisms in all of these animals with positive blood cultures were acquired fortuitously as has been previously described.[1, 2] The organisms recovered from the blood of these animals were identified as to species.

In the animals of groups 2, 3, 4, and 5, a temporary bacteremia was produced by the intentional intravenous injection of one of the three bacterial strains described below:

"Strain I.F.," which has been identified as a Lancefield group D strain of beta hemolytic streptococcus. This organism, originally chosen at random from a hospital laboratory for use in these experiments, had been isolated from a patient* with cholangitis and hepatic abscesses due to a malignant obstruction of the common bile duct. The colony count of a 24 hour broth culture of this organism ranged from 1,290,000,000 to 2,450,000,000 organisms per ml. with a mean of 1,500,000,000 per ml. We have previously reported[4] from this laboratory our experiences in the production of endocarditis using "Strain I.F."

The alpha hemolytic streptococcus (*Streptococcus viridans*) used in these experiments was isolated from the blood of a patient† with bacterial endocarditis and a congenital aorticopulmonary septal defect. The colony count of a 24 hour broth culture of this organism ranged from 13,000,000 to 178,000,000 organisms per ml. with a mean of 83,000,000 per ml.

The source of the coagulase negative staphylococcus used in these experiments cannot be traced. The mean colony count for this organism on a 24 hour broth culture was 1,500,000,000 organisms per ml.

All of the bacterial injections in this series of dogs were made intravenously using sterile syringes and a preparation of the skin indicated below. An injection of 0.05 ml. or 0.005 ml. of a 24 hour broth culture was made by diluting 1.0 ml. of the 24 hour broth culture to 10 ml. or to 100 ml. with normal saline, and then injecting 0.5 ml. of the resulting dilution. Blood cultures were made at frequent intervals by withdrawing 10 ml. of blood from the jugular vein into a sterile syringe after preparation of the skin using the following routine: shaving off the hair, soap and water, and then tincture of Zephiran (1:1000). One-half of this blood was placed in broth and the other half into 3.5 per cent sodium citrate solution for use in making pour plates for colony counts. The number of organisms per ml. of blood was roughly quantitated for all positive cultures. The beta hemolytic streptococcus (group D, "Strain I. F.") used in these experiments was tested for sensitivity to penicillin, Aureomycin, and streptomycin, and was found to be inhibited in vitro by the following concentrations of antibiotics:

* I. F., U. H. #817510
† G. M., U. H. #816233

penicillin	1.9 units per ml.
Aureomycin	7.8 μg per ml.
streptomycin	>62.5 μg per ml.
penicillin plus Aureomycin	1.9 units or μg. per ml. of each drug
penicillin plus streptomycin	3.9 units or μg. per ml. of each drug

Method of Study

All of the animals used in these studies were adult dogs of medium size of either sex, previously dewormed,* immunized against distemper,† and acclimated to the animal colony for four weeks before use. In the later experiments (groups 2 thru 5) the animals were also dipped at regular intervals in a parasiticide.‡ All dogs were fed a daily diet consisting of dog biscuits supplemented with fresh horsemeat and crude cod liver oil.

The technic used in the construction of the arteriovenous shunts has been described in earlier publications.[1, 2] Penicillin in oil (300,000 units per day) was given to each animal for one week after each surgical procedure.

Daily rectal temperatures and pulse rate determinations were taken during the preoperative control period and after the construction of the arteriovenous shunts. Daily auscultation of the fistulas was added to this routine in the postoperative interval.

In all dogs with arteriovenous fistulas, a negative blood culture was obtained before bacterial injections were begun. This precaution is essential because an occasional animal with bilateral arteriovenous shunts will be found to have acquired a bacteremia spontaneously during even a short postoperative interim.

A more detailed description of the experimental conditions pertaining to each of the six groups of dogs studied for the occurrence of glomerulonephritis follows:

Group 1. Dogs with Large Arteriovenous Fistula Loads Developing "Spontaneous" Endocarditis

The occurrence of endocarditis in dogs with large arteriovenous fistula loads without the necessity for intentional injection of bacteria has been referred to above. The reader is referred to earlier publications from this laboratory[1, 2] for details as to the size, location, and duration of the arteriovenous fistulas necessary for the observance of this endocarditis as well as for a more complete description of the experimental conditions for this group of animals. The dogs in this group were of two age groups, (1) young adult dogs of 2 to 5 years of age, (2) old dogs estimated to be 10 or more years of age. The influence of the dog's age upon endocarditis has been discussed previously.[1, 2]

Group 2. Dogs with Large Arteriovenous Fistulas Receiving Intravenous Injections of Beta Hemolytic Streptococcus (Group D)

All of the 11 animals in this group were 2 to 5 years of age and had bilateral arteriovenous fistulas made side to side from 10 mm. to 32 mm. in length between the arteries and veins of both lower extremities in the positions indicated in table 3. The shunts were constructed in stages usually a week or more apart. A recovery period of at least two weeks was allowed in all animals following the last surgical procedure for complete healing of the operative wounds and for the compensatory changes of the arteriovenous fistulas to take place before beginning the daily intravenous injections of beta hemolytic streptococcus (group D, "Strain I.F."). The dose of bacteria used was from 0.005 to 0.5 ml. of a 24 hour broth culture* per day from 2 to 19 days.

Group 3. Dogs with Large Arteriovenous Fistulas Receiving Intravenous Injections of an Alpha Hemolytic Streptococcus or Coagulase Negative Staphylococcus

The eight dogs in this group were exactly similar to those of group 2 except for the fact that following a similar recovery period after their last shunt operation, six animals received intravenously 0.005 to 0.5 ml. of a 24 hour broth culture of an alpha hemolytic streptococcus† per day for 7 to 22 consecutive days (group 3a). Two other animals in this group received 0.5 ml. per day for 10 to 55 days of a 24 hour broth culture of a coagulase negative staphylococcus (group 3b).‡

Group 4. Dogs with a Small Arteriovenous Fistula Load Receiving Intravenous Injections of a Beta Hemolytic Streptococcus. (Group D, "Strain I.F.")

The four dogs in this group all had a single short (10 to 11 mm.) femoral arteriovenous shunt. The postoperative period before bacterial injections were begun was intentionally varied from 4 to 30 days in order to assay the relative importance of varying durations of a small increase in cardiovascular stress in localizing the pathologic involvement to the heart valves and kidney glomeruli. Also, it was expected that the animals with a very short interval between construction of their arteriovenous shunt and the intravenous injection of bacteria might acquire an infection at their fistula site, and the consequent resulting continuous bacteremia plus a definite but small increase in cardiovascular stress (from the

* Vermiplex, Pitman-Moore Co., Div. Allied Laboratories Inc., Indianapolis, Ind.

† Virogen, Pitman-Moore Co., Div. Allied Laboratories Inc., Indianapolis, Ind.

‡ Lexone, E. I. du Pont de Nemours & Co. Inc., Wilmington, Del.

* Mean colony count = 1,500,000,000 organisms per ml.

† Mean colony count = 83,000,000 organisms per ml.

‡ Mean colony count = 1,500,000,000 organisms per ml.

single femoral arteriovenous fistula) would provide a test of the relative importance of these factors in localizing bacterial involvement to the valve leaflets and kidneys. Each of the dogs in this group was given a daily intravenous dose of 0.5 ml. of beta hemolytic streptococci* (group D, "Strain I.F.") for seven consecutive days.

Group 5. A Group of Normal Control Animals

These control dogs were similar in all respects to groups 2 through 4 except for the absence of arteriovenous fistulas. These normal dogs received intravenous injection in the amounts indicated below of one or more of the same three strains of bacteria used for the experiments involving groups 2, 3, and 4.

(a) Beta hemolytic streptococcus (group D, "Strain I.F.") in intravenous doses varying from 0.5 to 50.0 ml. per day of a broth culture* for periods varying from 7 to 15 consecutive days.

(b) Coagulase negative staphylococcus in intravenous doses varying from 0.5 to 1.0 ml. of a 24 hour broth culture* per day for from 16 to 48 successive days.

(c) Alpha hemolytic streptococcus in intravenous doses of 0.5 ml. of a 24 hour broth culture† for 7 to 42 consecutive days.

Group 6. Dogs from the Animal Colony

Dogs from the same animal colony, which had been used in a wide variety of other experiments, were subjected to a careful autopsy, and their hearts and kidneys studied grossly and microscopically to determine the incidence of glomerulonephritis and/or endocarditis in our animal colony.

Pathology

Each of the animals reported upon in this paper had a complete autopsy performed at the time of death. Blocks were cut from both kidneys as well as from other organs and fixed immediately in 10 per cent formalin. The paraffin tissue sections have been stained routinely with hematoxylin and eosin. Azocarmine stains also have been utilized to demonstrate changes in the connective tissue elements. The term proliferative glomerulonephritis is used to describe a proliferative reaction of the glomerular endothelium with resulting obstruction of the capillaries. The glomerular lesions occurring in these animals have been graded 1 plus to 3 plus on the following basis:

Glomerulonephritis grade 1 plus consists of a diffuse involvement of all or virtually all of the glomeruli visible in the stained sections by a definite increase in the number and size of endothelial cells lining the capillaries. Microscopically, under low magnification, the glomeruli appear densely cellular and few or no erythrocytes are to be seen.

Grade 3 plus consists of a severe involvement of all the glomeruli characterized by a proliferation of endothelial cells to such a degree that all the capillaries are partially or completely obstructed.

Grade 2 plus was applied to the glomerular lesions intermediate in severity between these two categories.

It is emphasized that in several dogs classified as negative, there was seen a definite endothelial cell proliferation in some glomeruli, but the majority of the glomeruli were not involved. It is considered quite likely that those animals with lesser degrees of involvement represent an early stage of the same pathologic process.

Results

The over-all incidence of glomerulonephritis in relationship to these varying experimental conditions outlined above is summarized in table 1. It is significant that all of the 11 animals developing glomerulonephritis in our experiments were dogs with large arteriovenous fistula loads (groups 1, 2, and 3a). The incidence of glomerulonephritis in each of these three groups was rather constant, varying only from 33 to 50 per cent. With two exceptions (dogs 1042 and 1318, table 4) all of the dogs with glomerulonephritis had endocarditis. All of the 11 dogs developing glomerulonephritis had a lesion classified as acute diffuse proliferative glomerulonephritis, characterized by an intracapillary proliferation of the glomerular endothelium with resulting obstruction of the capillaries. Seven (64 per cent) of the dogs were classified as 1 plus, indicating a definite widespread partial capillary obstruction by endothelial cell hypertrophy and hyperplasia. Figures 3 and 4 are low and higher power photo micrographs indicating the histologic appearance of the kidneys classified as 1 plus glomerulonephritis. These changes may be compared with the appearance of normal canine kidneys

* Mean colony count = 1,500,000,000 organisms per ml.

† Mean colony count = 83,000,000 organisms per ml.

under similar magnification (figs. 1 and 2). Two dogs (18 per cent) had a more severe degree of capillary obstruction and were classified as 2 plus glomerulonephritis. Two animals (18 per cent) had a severe and widespread degree of capillary obstruction classified 3 plus. Figures 5 and 6*A* and *B* indicate the histologic features of the kidneys so classified. The cells of the tubules showed no noteworthy changes although the lumens of the tubules contained a few casts. There were no cases of focal or embolic glomerulonephritis observed in these dogs in spite of the fact that nearly all of them had a bacteremia and endocarditis. A similar occurrence of diffuse glomerulonephritis associated with bacterial endocarditis in humans has been described.[5] In none of the kidneys with glomerulonephritis was it possible to demonstrate microscopically the presence of bacteria in the tissues.

The incidence of glomerulonephritis in relationship to the bacterial species was as follows (table 1): Four were caused by a beta hemolytic streptococcus (group D, "Strain I.F."), four were caused by an alpha hemolytic streptoccus, two by a coagulase positive staphylococcus and one dog had no cultures.*

The diagnosis of glomerulonephritis in these animals was frequently suggested before death by the observation of gross hematuria. At autopsy, the kidneys showed grossly only swelling.

Among the 12 dogs with large arteriovenous fistula loads developing endocarditis without the intentional injection of bacteria (group 1), there were four (33 per cent) animals developing acute diffuse proliferative glomerulonephritis (table 2). The infecting organism, in each case spontaneously acquired, was in two of the animals (dogs 177, 1737) a coagulase positive staphylococcus, in the third animal (dog 114) was a streptococcus viridans, and the fourth dog (dog 6)* did not have blood cultures drawn. Photographs of the heart valve lesions asso-

TABLE 1.—*Incidence of Glomerulonephritis in Relation to Cardiovascular Stress Summary*

Amount of Cardiovascular Stress	No. Dogs	Acute Diffuse Proliferative Glomerulonephritis					Etiologic Organism			
		Incidence		Grade			Beta Hemolytic Strep.*	Strep. Viridans	Coag.+ Staph.	Unknown
		No.	%	1+	2+	3+				
Group 1: Large Arteriovenous Fistula Loads with Endocarditis occurring spontaneously	12	4	33	2	1	1		1	2	1
Group 2: Bilateral Arteriovenous Fistulas with I.V. injection of Beta Hemolytic Strep.*	11	4	36	2	1	1	4			
Group 3a: Bilateral Arteriovenous Fistulas with I.V. injection of Strep. Viridans	6	3	50	3				3		
Group 3b: Bilateral Arteriovenous Fistulas with I.V. injection of Coag. Neg. Staph.	2	0	0							
Group 4: Single Short Femoral A.V.F. with I.V. injection of Beta Hemolytic Strep.*	4	0	0							
Group 5: None (Normal Dogs with I.V. injection of Beta Hemolytic Strep.,* Strep. Viridans, or Coag. Neg. Staph.)	10	0	0							
Group 6: None (Dogs from our animal colony used in other experiments)	36	0	0							
Total		11		7	2	2	4	4	2	1

* Lancefield group D, "Strain I.F."

*At autopsy a blood culture taken from the inferior vena cava disclosed a mixed growth of alpha hemolytic streptococcus, *Aerobacter aerogenes*, and proteus in this animal (dog 6).

FIG. 1. Normal (dog) kidney, H & E stain, photomicrograph × 150.

FIG. 2. A normal (dog) glomerulus, H & E stain, photomicrograph × 450.

ciated with the glomerulonephritis in two of these animals (dogs 114, 6) have been previously published.[1, 2] It is perhaps noteworthy that although *Aerobacter aerogenes* was the organism most frequently responsible for the endocarditis in this particular group of animals, there were no instances of this organism causing glomerulonephritis. In this group of dogs, the time interval from the construction of the arteriovenous shunts until death of the animal

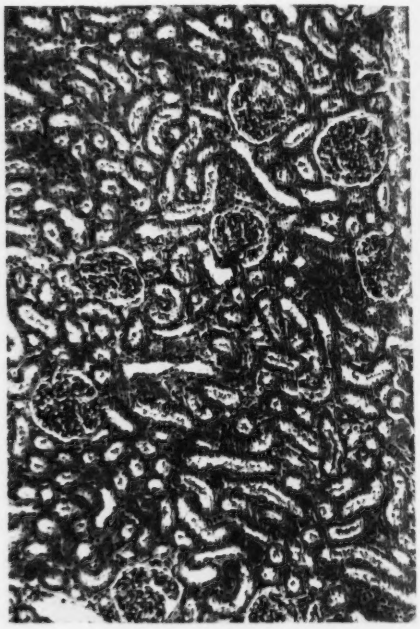

FIG. 3. Dog 1042. Acute diffuse proliferative glomerulonephritis grade 1 plus, note: the cellular proliferation in all of the visible glomeruli, H & E stain, photomicrograph × 150.

in those dogs developing acute glomerulonephritis varied from a minimum of 14 days (dog 177) to a maximum of about two and one-half months (dog 1737).

There have been 13 additional dogs (not listed in table 2) which have had arteriovenous fistula loads of magnitude comparable to the animals of group 1, and whose fistulas had existed for 14 days or more. These animals represent dogs that died of heart failure without endocarditis or were sacrificed deliberately before the development of endocarditis in order to determine the effect of arteriovenous fistulas upon adrenal gland weight. None of these 13 animals without endocarditis had glomerulonephritis.

FIG. 4. Dog 1042. Closeup of a glomerulus (from fig. 3) with acute diffuse proliferative glomerulonephritis grade 1 plus. Note that the capillaries are partially blocked by the hypertrophy and hyperplasia of the endothelial cells, H & E stain, photomicrograph × 450.

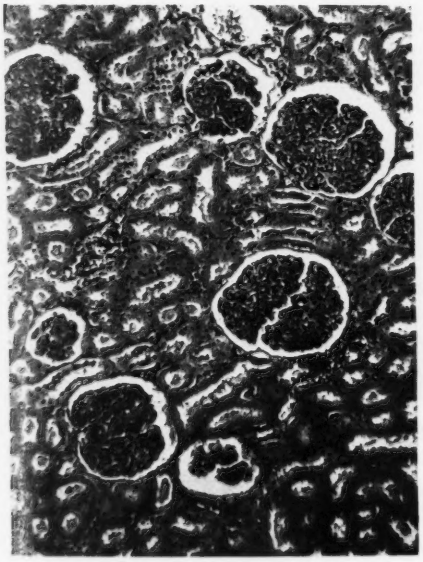

FIG. 5. Dog 114. Acute diffuse proliferative glomerulonephritis grade 3 plus. Note the large cellular glomeruli, H & E stain, photomicrograph × 150.

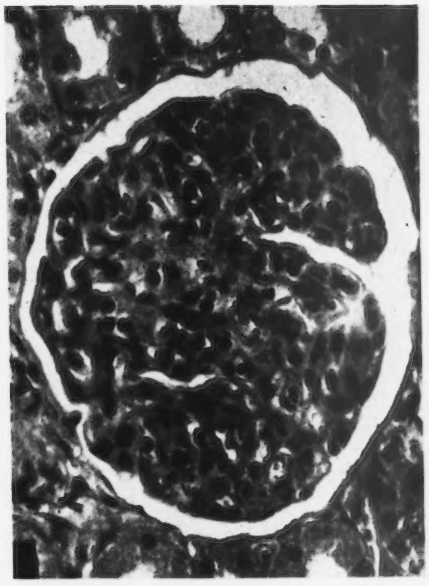

FIG. 6*A*

FIG. 6*B*

FIG. 6. Dog 114. A glomerulus (from fig. 5) with acute diffuse proliferative glomerulonephritis grade 3 plus. *A*. Note the complete capillary obstruction. No erythrocytes are seen, H & E stain, photomicrograph × 450. *B*. Note the capillaries are completely blocked by large endothelial cells. Azocarmine stain, photomicrograph × 450.

TABLE 2.—*Incidence of Glomerulonephritis in Dogs with Large Arteriovenous Fistula Loads Acquiring "Spontaneous" Endocarditis**

Dog No.	Age	Arteriovenous Fistulas			Acute Diffuse Proliferative Glomerulonephritis Grade†	Organism Acquired	Blood Culture (Maximum colonies per ml.)	Result	Comment
		Location	Length mm.	Duration Days					
177	Young	Iliac	30	14	2+	Coag. + Staph.	1320	Died, Glomerulonephritis & Endocarditis	Abscess in laparotomy wound
114	Young	Iliac Femoral	27 25	42 30	3+	Strep. viridans	>600	Died, Glomerulonephritis & Endocarditis	
6	Old	Iliac	25	55	1+	Not done	—	Died, Glomerulonephritis & Endocarditis	
37	Old	Femoral Femoral	31 31	81 69	0	Aerobacter aerogenes	>300	Died, Endocarditis	
1737	Young	Iliac Femoral	21 24	82 31	1+	Coag. + Staph.	6500	Died, Glomerulonephritis & Endocarditis	
250	Young	Iliac‡ Aorta-Cava	30 15	98 60	0	Not done	—	Died, Endocarditis	
36	Old	Iliac Femoral	15 30	87 109	0	Aerobacter aerogenes	45	Sacrificed,§ Endocarditis	Iliac A.V.F. Closed at autopsy
124	Young	Iliac Femoral	25 23	109 76	0	Not done	—	Died, Endocarditis	
451	Young	Iliac Iliac	25 31	112 27	0	Not done	—	Died, Endocarditis	
26	Young	Iliac Femoral	29 31	120 35	0	Aerobacter aerogenes	>300	Died, Endocarditis	
35	Young	Iliac Femoral	33 18	121 63	0	Aerobacter aerogenes	1000	Died, Endocarditis	
24	Young	Iliac Femoral	30 31	148 137	0	Beta Hemolytic Streptococcus	1000	Died, Endocarditis	

* Animals of group 1 in text
† Graded on basis of 1+ to 3+
‡ Iliac A.V.F. partially closed prior to making aorta-cava shunt
§ Treated with Aureomycin
No. of dogs with endocarditis — 13; No. of dogs with acute diffuse proliferative glomerulonephritis — 4

In the 11 animals of group 2 with large arteriovenous fistulas and receiving intravenous as has been studied, between the number of bacteria injected or the duration of the endo-

TABLE 3.—*Incidence of Glomerulonephritis with Bilateral Arteriovenous Fistulas and Bacterial Injection**
Beta Hemolytic Streptococcus (Lancefield Group D, "Stain I. F.")

Dog No.	Sex	Arteriovenous Fistulas			Dose† (24 hour broth culture) ml./day I. V.	No. Days Injected	Result	Acute Diffuse Proliferative Glomerulonephritis Grade‡	Comment	Days Duration of Life from First Bacterial Injection until Death.
		Location	Length mm.	Days Duration at Start of Bacteria Injection						
1194	F	Iliac Iliac	21 14	35 32	0.005	7	Sac.	1+	Endocarditis	27
1339	F	Iliac Femoral	17 15	16 18	0.005	19	"	0	"	65
60	M	Iliac Iliac	20 10	133 45	0.05	2	Died	3+	"	42
1293	M	Iliac Femoral	18 13	22 25	0.05	7	Sac.	0	"	64
56	M	Iliac Femoral	23 17	137 14	0.05	7	Died	0	"	61
1460	M	Iliac Femoral	26 17	16 14	0.5	6	"	0	"	18
779	F	Iliac Femoral	24 18	17 20	0.5	7	"	0	"	25
70	M	Iliac Femoral	29 25	286 17	0.5	7	Died§	1+	"	15
100-x	M	Iliac Femoral	30 15	278 142	0.5	7	Died§	2+	"	25
1886	F	Iliac Femoral	25 20	23 77	0.5	7	Died‖	0	"	48
718	M	Iliac Femoral	32 21	17 14	0.5	10	Died	0	"	17

* Animals of group 2 in text.

† Mean colony count on a 24 hour broth culture = 1,500,000,000 organisms per ml.

‡ Graded on a basis of 1+ to 3+.

§ The endocarditis was treated with penicillin and Aureomycin in therapeutic doses before death.

‖ The endocarditis was treated with penicillin, Aureomycin, streptomycin, in therapeutic doses, and both arteriovenous fistulas were excised 23 days before death.

No. of animals with arteriovenous fistulas injected = 11; No. of animals with diffuse proliferative glomerulonephritis = 4.

injections of beta hemolytic streptococcus (group D, "Strain I.F."), there were four (36 per cent) that developed acute proliferative glomerulonephritis. Inspection of table 3 does not suggest any particular relationship, as far carditis and the occurrence of glomerulonephritis. However, it should be noted that two (dogs 70, 100-x) of the three animals receiving large doses of antibiotics as treatment for their endocarditis developed glomerulonephritis. A photo-

graph of the heart valve lesions associated with the glomerulonephritis in dog 100-x has been published.[4] Likewise, both of the two animals (dogs 1194, 60) with bilateral iliac arteriovenous fistulas had both glomerulonephritis and endocarditis. The significance of this observation, if any, will have to be determined by future experiments. Table 6 contains the results of the blood cultures for the four dogs of this group developing glomerulonephritis. It will be noted on inspection of these results that all of these animals developing glomerulonephritis had profound septicemias. However, a similar septicemia, as has been previously reported,[4] occurred as well in those animals of this group that developed endocarditis without glomerulonephritis. The incidence of endocarditis in this group has been 100 per cent.

Of the six dogs with large arteriovenous fistula loads receiving varying doses of an alpha hemolytic streptococcus (group 3a) intravenously, three (50 per cent) developed glomerulonephritis and two developed endocarditis (table 4). However, two of the dogs with glo-

TABLE 4.—*Incidence of Glomerulonephritis with Bilateral Arteriovenous Fistulas and Bacterial Injection** Alpha Hemolytic Streptococcus or Coagulase Negative Staphylococcus

Dog No.	Sex	Arteriovenous Fistulas			Organism	Dose (24 hr. Broth Culture) ml./day. I.V.	No. of Days	Result	Acute Diffuse Proliferative Glomerulonephritis Grade†	Comment	Days Duration of Life from First Bacterial Injection until Death
		Location	Length mm.	Days Duration at Start of Bacterial Injections							
1277	M	Iliac Femoral	14 19	17 14	Alpha Hem. Strep.‡	0.005	7	Sac.	0	No Endocarditis	32
1318	F	Iliac Femoral	13 17	20 16	Alpha Hem. Strep.‡	0.005	7	Sac.	1+	No Endocarditis	68
1361	F	Iliac Femoral	17 15	15 18	Alpha Hem. Strep.‡	0.05	7	Sac.	0	No Endocarditis	63
1042	F	Iliac Iliac	15 17	16 14	Alpha Hem. Strep.‡	0.05	7	Sac.	1+	No Endocarditis, Infected Vegetations on A.V.F. site	29
62	M	Iliac Iliac	20 19	138 14	Alpha Hem. Strep.‡	0.5	7	Died	0	Endocarditis	16
81	M	Iliac Femoral	20 24	22 63	Alpha Hem. Strep.‡	0.5	22	Died	1+	"	56
745	M	Iliac Femoral	20 18	18 14	Coag. Neg.§ Staph.	0.5	10	Died	0	"	28
98	F	Iliac Femoral	23 22	23 22	Coag. Neg.§ Staph.	0.5	55	Sac.	0	No Endocarditis	145

* Animals of groups 3a and 3b in text.

† Graded on basis of 1+ to 3+.

‡ Mean colony count on a 24 hour broth culture = 83,000,000 organisms per ml.

§ Mean colony count on a 24 hour broth culture = 1,500,000,000 organisms per ml.

No. of dogs with arteriovenous fistulas injected = 8; No. of dogs with diffuse proliferative glomerulonephritis = 3.

nerulonephritis (dogs 1318, 1042) did not have ndocarditis, but dog 1042 did have an infected egetation at the arteriovenous fistula site. The esults of the blood cultures taken on these hree dogs with glomerulonephritis (dogs 81, 042 and 1318) are summarized in table 6.

(group D, "Strain I.F.") for seven days did not cause endocarditis, or glomerulonephritis, nor were there any other apparent ill effects. The results in this group of animals have been discussed in more detail in a previous publication[4] in relationship to endocarditis. The zero

TABLE 5.—*Bacterial Injection into Normal Dogs**

Dog No.	Type of Bacteria	Dose (24 Hr. Broth Culture) ml./day I.V	No. of days injected	Results	Glomerulonephritis or Endocarditis
1162	Beta Hem. Strep.†	0.5	7	Sacrificed	None
198	Beta Hem. Strep.†	2.0	7	"	"
1887	Beta Hem. Strep.†	0.5	7	"	"
		2.0	7	"	"
386	Beta Hem. Strep.†	50.0	6	"	"
277	Beta Hem. Strep.†	50.0	7	"	"
294	Beta Hem. Strep.†	50.0	7	"	"
963	Coag. Neg. Staph.‡	0.5	16	"	"
	Coag. Neg. Staph.‡	1.0	34		
	Beta Hem. Strep.†	0.5	14		
989	Coag. Neg. Staph.‡	0.5	48	"	"
	Alpha Hem. Strep.§	0.5	7		
	Beta Hem. Strep.†	0.5	15		
1327	Alpha Hem. Strep.§	0.5	42	"	"
1362	Alpha Hem. Strep.§	0.5	4	"	"
		0.5	40		

* Animals of group 5 in text

† Lancefield group D, "Stain I.F."; mean colony count = 1,500,000,000 organisms per ml. of a 24 hour broth culture

‡ Mean colony count = 1,500,000,000 organisms per ml. of a 24 hour broth culture

§ Mean colony count = 83,000,000 organisms per ml. of a 24 hour broth culture

No. of normal dogs injected = 10; No. of normal dogs developing glomerulonephritis (or endocarditis) = 0

Two additional animals (dogs 745, 98) in this group (3b) with bilateral arteriovenous shunts received intravenous injections of a coagulase negative staphylococcus, and although one developed endocarditis, neither showed glomerulonephritis.

In the four dogs with a single short femoral arteriovenous fistula (group 4), the daily intravenous injection of a 0.5 ml. of a 24 hour broth culture* of beta hemolytic streptococcus

* Mean colony count = 1,500,000,000 organisms per ml.

incidence of glomerulonephritis and endocarditis in these animals with only a small increase in cardiovascular stress are in direct contrast to the 36 per cent incidence of glomerulonephritis and the 100 per cent incidence of endocarditis (group 2) that was observed in the dogs with large increases in cardiovascular stress (bilateral arteriovenous fistulas) receiving bacterial doses of comparable magnitude. It should also be noted that, as anticipated, in the two dogs with femoral fistulas of only four and six days duration (dogs 120, 1918) it

TABLE 6.—*Blood Cultures in Dogs with Glomerulonephritis Produced by Large Arteriovenous Fistula Loads and Bacterial Injection*

Dog No.	Amount of Cardiovascular Stress	Type of Bacteria	Total I.V. Bacterial Dose* (24 hr. Broth Culture) ml.	Dates of Bacteria Injections	Results of Blood Cultures		Remarks
					Date	No. of organisms per ml. of blood	
1194	Bilateral Iliac A.V.F.	Beta Hem. Strep.†	0.035	7/19–7/25 inc.	7/14 7/31 8/7 8/14	Negative 596 Beta Strep. 1800 Beta Strep. 1600 Beta Strep.	Sacrificed 8/14, Endocarditis
60	Bilateral Iliac A.V.F.	Beta Hem. Strep.†	0.10	7/15–7/16 inc.	7/14 7/17 7/24 8/8 8/15 8/23	33 Gram + Cocci 15 Beta Strep. 272 Beta Strep. 124 Beta Strep. 340 Beta Strep. 4266 Beta Strep.	Note: This dog had bacteremia before bacterial injections were started. Died 8/25, Endocarditis
70	Iliac and Femoral A.V.F.	Beta Hem. Strep.†	3.5	1/3–1/9 inc.	1/2 1/11 1/12 1/18§	Negative 27 Beta Strep. 639 Beta Strep. 1457 Beta Strep.	1/16 to 1/18 received a daily dose of: Penicillin—800,000 units; Aureomycin—1.5 Gm. 1/18 Died, Endocarditis
100–x	Iliac and Femoral A.V.F.	Beta Hem. Strep.†	3.5	12/13–12/19 inc.	12/22 12/23 1/2 1/5§	2102 Beta Strep. 5040 Beta Strep. 3148 Beta Strep. 2556 Beta Strep.	1/4 to 1/6 received a daily dose of: Penicillin—700,000 units; Aureomycin—1.5 Gm. 1/6 Died, Endocarditis
81	Iliac and Femoral A.V.F.	Alpha Hem. Strep.‡	11.0	3/23-4/13 inc.	3/14 4/11 4/20 5/10 5/17	Negative 106 Alpha Strep. 16 Alpha Strep. 280 Alpha Strep. Positive Alpha Strep.	5/17 Died, Endocarditis
1042	Bilateral Iliac A.V.F.	Alpha Hem. Strep.‡	0.35	7/17–7/23 inc.	7/17 7/31 8/7 8/14	No growth 120 Alpha Strep. 62 Alpha Strep. 413 Alpha Strep.	Infected vegetations on A.V.F. site. Sacrificed 8/14, no Endocarditis
1318	Iliac and Femoral A.V.F.	Alpha Hem. Strep.‡	0.035	7/17 and 7/20–7/25 inc.	7/17 7/31 8/1 8/2 8/9 8/14 8/21	Negative 2 Alpha Strep. 54 Alpha Strep. 74 Alpha Strep. Positive Alpha Strep. 2 Alpha Strep. 1 Alpha Strep.	9/22 Sacrificed, no endocarditis, both A.V.F. were open and free of infection

* Total Bacteria Dose = daily dose of a 24 hr. broth culture in ml. multiplied by the no. of days injected.

† Lancefield group D, "Strain I.F."; mean colony count = 1,500,000,000 organisms per ml. of a 24 hr. broth culture.

‡ Mean colony count = 83,000,000 organisms per ml. of a 24 hr. broth culture.

§ Animal receiving antibiotic therapy at time blood culture was drawn.

is quite likely that the fistula became the site of a localized infection. This conclusion is based on the fact that in both of these animals the blood cultures (table 7) indicated a significant elevation (up to 381 organisms per ml. in dog 1918, and up to 24 organisms per ml. in dog 120) above the usual degree of bacteremia. Nevertheless, even in the presence of this temporary septicemia without an appreciable increase in cardiovascular stress, there was no tendency for the bacterial infection to involve the endothelium of the kidneys or heart, and the blood cultures gradually became sterile again.

The results (table 5) of the injection of these same bacterial strains into normal dogs (group 5) are also in distinct contrast to the results observed in dogs with bilateral arteriovenous shunts. In the normal dogs, the intravenous injection of several different species of bacteria as indicated in table 5 caused no apparent ill effects except the transient occurrence of fever. All of the animals remained in excellent health, and it was necessary to sacrifice them for autopsy. There was no glomerulonephritis or endocarditis found. It will be noted (table 7) that the blood cultures in these animals nearly always revealed a low-grade bacteremia for the first few days immediately after the cessation of a course of bacterial injections. However, after this short interval, their blood streams became sterile again in all cases. It should be noted that the total numbers of beta hemolytic streptococci (group D, "Strain I.F.") organisms injected into these normal control animals were as much as 10,000 times greater than the minimum number of organisms necessary to produce glomerulonephritis in the dogs with bilateral arteriovenous shunts. Likewise, in the case of the alpha hemolytic streptococcus the numbers of bacteria that were injected into the normal dogs were as much as 620 times the minimum number of bacteria necessary to cause glomerulonephritis in the dogs with bilateral arteriovenous fistulas. These comparisons in numbers of organisms provide striking evidence of the importance of the physiologic alterations associated with large arteriovenous fistulas in promoting endothelial susceptibility to infection.

As indicated in table 1, the gross and microscopic study of the kidneys and hearts from 36 consecutive dogs (group 6) from our animal colony which had been used in a wide variety of other experiments did not disclose any instance of glomerulonephritis or endocarditis. A number of these dogs were subjected to surgical operations and some of them also had complicating wound infections with no apparent tendency for localization of the infection to the kidney glomeruli or heart valves. Our findings of the rarity of glomerulonephritis in normal dogs and the relative frequency of the easily distinguishable interstitial nephritis were similar to those of others.[7, 8]

Discussion

Several comprehensive surveys of the literature on experimentally induced lesions of the kidney have been published[9, 10] in recent years, which indicate the large number of attempts that have been made to reproduce the human disease, glomerulonephritis. Of the numerous methods that have been tried for the experimental production of glomerulonephritis, those involving bacteria or the products of their growth and those involving some form of hypersensitivity to a protein appear to have invoked the greatest interest and produced the closest approach to human lesions. However, Simonds and co-workers[11] and McNider,[9] among others, have expressed the general discouragement with the results obtained by the use of either living or dead bacteria or their toxins for the experimental production of diffuse glomerulonephritis. These unsatisfactory results are made even more difficult to understand because of the intimate association clinically of bacterial infection with the pathogenesis of glomerulonephritis. Loeb[12] and Horn[10] concluded from a review of the literature that diffuse glomerulonephritis satisfying all of the criteria required for the diagnosis of the human disease had not yet been produced experimentally by any method.

The present experiments provide a new approach to this problem. By utilizing the cardiovascular stress of large arteriovenous fistula loads together with a bacteremia occurring either by the fortuitous entrance of bacteria

TABLE 7.—*Blood Cultures in Normal* Dogs and Dogs with Small* Arteriovenous Fistula Loads Receiving Bacterial Injections*

Dog No.	Amount of Cardiovascular Stress	Type of Bacteria	Total I.V. Bacteria Dose† (24 Hr. Broth Culture) ml.	Dates of Bacteria Injections	Results of Blood Cultures		Remarks
					Date	No. organisms per ml. blood	
120	Single Short Femoral A.V.F.	Beta Hemolytic Strep.‡	3.5	12/3–12/9 inc.	12/11 12/12 12/15 1/3	Negative Negative 24 Beta Strep. Negative	1/3 A.V. Fistula still open. 1/22/51, Sacrificed
1918	Single Short Femoral A.V.F.	Beta Hemolytic Strep.‡	3.5	11/30–12/6 inc.	12/7 12/8 12/15 1/3	209 Beta Strep. 381 Beta Strep. 9 Beta Strep. Negative	12/28 A.V. Fistula closed spontaneously. 1/23, Sacrificed
119	Single Short Femoral A.V.F.	Beta Hemolytic Strep.‡	3.5	11/30–12/6 inc.	12/7 12/8 12/15 1/3	Negative 1 Beta Strep. Negative Negative	12/15 A.V. Fistula open. 1/15, Sacrificed
814	Single Short Femoral A.V.F.	Beta Hemolytic Strep.‡	3.5	11/30–12/6 inc.	12/7 12/8 12/14	1 Beta Strep. 1 Beta Strep. Negative	12/8 A.V. Fistula open. 1/13 Sacrificed
1162	None (had a femoral A.V.F. which closed)	Beta Hemolytic Strep.‡	3.5	11/30–12/6 inc.	12/7 12/8 12/15 1/3	1–2 Beta Strep. 1–2 Beta Strep. Negative Negative	1/19 Sacrificed
198	None (Normal Dog)	Beta Hemolytic Strep.‡	14.0	1/2–1/8 inc.	1/2 1/10 1/11 1/17 1/23 2/5	Negative 5 Beta Strep. 5 Beta Strep. Negative Negative Negative	2/5 Sacrificed
1887	None (Normal Dog)	Beta Hemolytic Strep.‡	3.5 14.0 17.5	12/2–12/8 inc. 1/3–1/9 inc.	12/11 12/12 12/14 1/11 1/12 1/17	1 Beta Strep. Negative Negative 1–2 Beta Strep. 1–2 Beta Strep. Negative	1/23 Sacrificed
386	None (Normal Dog)	Beta Hemolytic Strep.‡	300	1/31–2/6 inc.	None	—	2/7 Sacrificed

* No glomerulonephritis (or endocarditis) was observed in any of these animals.

† Total bacteria dose = daily dose (in ml.) of a 24 hour broth culture multiplied by no. of consecutive days injected.

‡ Lancefield group D, "Strain I.F.," average colony count on a 24 hour broth culture of this organism = 1,500,000,000 bacteria per ml.

§ Average colony count on a 24 hr. broth culture of this organism = 1,500,000,000 bacteria per ml.

‖ Average colony count on a 24 hr. broth culture of this organism = 83,000,000 bacteria per ml.

TABLE 7.—*Continued*

Dog No.	Amount of Cardiovascular Stress	Type of Bacteria	Total I.V. Bacteria Dose† (24 hr. Broth Culture) ml.	Date of Bacteria Injections	Results of Blood Cultures		Remarks
					Date	No. organisms per ml. blood	
277	None (Normal Dog)	Beta Hemolytic Strep.‡	350.0	1/10–1/16 inc.	1/19 1/22 1/29	1–2 Beta Strep. Negative Negative	1/30 Sacrificed
294	None (Normal Dog)	Beta Hemolytic Strep.‡	350.0	1/24–1/30 inc.	2/2 2/5 2/9	9 Beta Strep. Negative Negative	3/6 Sacrificed
963	None (Normal Dog)	Coag. Neg. Staph.§ Coag. Neg. Staph.§ Beta Hemolytic Strep.‡	8.0 34.0 7.0	5/27–6/11 inc. 6/12–7/13 inc. 8/8–8/21 inc.	7/14 8/28	Negative Negative	9/22 Sacrificed
989	None (Normal Dog)	Coag. Neg. Staph.§ Strep. Viridans‖ Beta Hemolytic Strep.‡	24.0 3.5 7.5	5/27–7/13 inc. 7/21–7/27 inc. 8/7–8/21 inc.	7/14 8/28	Negative Negative	8/28 Sacrificed
1327	None (Normal Dog)	Strep. Viridans‖	21.0	7/13–8/23 inc.	7/24 7/27 7/31 8/28	Negative Negative Negative Negative	8/28 Sacrificed
1362	None (Normal Dog)	Strep. Viridans‖ Strep. Viridans‖	2.0 20.0	7/13–7/16 inc. 7/21–8/31 inc.	None		9/22 Sacrificed

into the animal's blood stream, or produced by the intravenous injection of small numbers of bacteria, it has been possible to produce in one-third of the dogs studied an acute diffuse proliferative glomerulonephritis which satisfied many of the criteria required for diagnosis of the human disease.

The fact that the glomerulonephritis occurred in a rather constant percentage of the dogs of groups 1, 2, and 3, in contrast to the close to 100 per cent incidence of endocarditis suggests that some rather constantly occurring, but at present unknown, factor is necessary for the occurrence of glomerulonephritis in addition to bacterial infection and cardiovascular stress. No studies have as yet been made to determine whether individual differences among the several animals in their immune reactions to foreign proteins of bacterial origin may account for failure of all dogs treated similarly to respond alike. Furthermore, there may be such large individual differences in the endocrine and metabolic responses to the conditions imposed as to account for the nonuniformity of behavior.

It is important to emphasize that the dogs used in these experiments had a high protein diet of excellent quality. Smadel and Farr[13] showed a significant correlation between protein intake and susceptibility to a nephrotoxic

lesion in rats. The other details of experimental technic in the study reported have been described fully because of the possibility that precisely similar conditions may be necessary to the reproduction of the results. Since the importance of many of the variables has not been tested by controlled experiments, it is impossible to state which of the conditions employed, other than those which have been analyzed, are or are not necessary to the result obtained.

In persons dead of bacterial endocarditis, nearly one-half show a moderate increase of glomerular endothelium with partial capillary obstruction (grade 1) and in a small percentage there is a severe capillary obstruction by endothelium (grade 3) which is clinical acute glomerulonephritis. Therefore, the acute glomerulonephritis in dogs must in some way be related to the bacteremia which was associated in most but not all of the animals with endocarditis. The intimate mechanism by which bacteremia produces glomerulonephritis is not understood; but, nevertheless, by combining the effects of a cardiovascular stress with bacteremia, a method has been found by which glomerulonephritis may be produced experimentally. This experimental glomerulonephritis corresponds entirely in its histologic features with the human lesion.

Conclusions

1. Acute diffuse proliferative glomerulonephritis has been found in about one-third of dogs with large arteriovenous anastomoses in which endocarditis occurred either with intentional or adventitious introduction of pathogenic organisms.

2. The majority of the dogs showed the lesions in "early" phases of the disease—two were moderately severe and two very severe—indistinguishable from those seen in patients dying from acute diffuse proliferative glomerulonephritis.

3. In a series of 36 control dogs without arteriovenous fistulas and without bacterial injection, no case of glomerulonephritis was found upon microscopic examination.

4. Ten unoperated normal dogs were given injections of 620 to 10,000 times the numbers of bacteria of the same species and strains as were followed by kidney lesions in dogs with bilateral large arteriovenous fistulas. There was in no case either endocarditis or glomerulonephritis in these normal dogs.

5. In dogs with single small femoral anastomoses receiving intravenous injections of bacteria in comparable numbers neither endocarditis nor glomerulonephritis occurred.

6. Glomerulonephritis was observed in association with infection by alpha and beta hemolytic streptococcus and coagulase positive staphylococcus. The lesion is therefore not limited in the dog to a single strain. No case was observed in association with *Aerobacter aerogenes* or coagulase negative staphylococcus endocarditis in six dogs.

7. Because of the absence of lesions in the unoperated normal dogs and dogs with small fistulas given the same bacteria in the same or much larger numbers than given to the animals with large fistulas subsequently showing glomerulonephritis, it is concluded that the cardiovascular stress plays a major role in determining the susceptibility of dogs to glomerulonephritis.

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The Quantitative Electrokymograph

By Russell H. Morgan, M.D. and Ralph E. Sturm

The quantitative electrokymograph has been developed in an effort to provide an instrument which will be easier to operate than the electrokymographic equipment currently available. In addition, provision has been made for the recording of both border-motion phenomena and densitometric changes within the heart and great vessels. In the design of the instrument, considerable attention has been directed toward the development of a means whereby electrokymographic tracings may be calibrated. Care has also been exercised in the instrument's design in order to provide a frequency response that is essentially flat from 0 to 40 cycles per second.

SINCE its development a few years ago,[1] the electrokymograph has been used by a number of workers to study the border motions of the heart and great vessels. Early investigations have been concerned primarily with an examination of the normal movements of these structures.[2, 3] More recently, however, the study of a number of pathologic states has been undertaken. Characteristic electrokymographic tracings have now been identified in myocardial infarction,[4, 5] constrictive pericarditis,[6] a variety of valvular lesions,[7–10] and ventricular and aortic aneurysms.[11]

In addition to its use in the study of border motions, the electrokymograph has been applied to a limited extent in the recording of densitometric changes within the heart and lungs. By these densitometric studies, it has been possible to estimate cardiac output[12] and pulmonary arterial pressure[13] with some success.

Although much good work has been done with the electrokymograph, a number of deficiencies within the instrument have seriously limited its application. First, it has not been possible to calibrate the amplitudes of electrokymographic tracings in terms of the physiologic phenomena which have produced them. This applies not only when one has used the instrument to record cardiac and vascular border motions, but also when one has applied the device to study the densitometric changes of a structure. Consequently, most of the work done with the electrokymograph has been qualitative in nature rather than quantitative.

Another defect of current electrokymographic apparatus is the limited frequency response which it provides. At the First Electrokymographic Conference, sponsored and conducted by the National Heart Institute in Bethesda, Maryland in May, 1950, it was reported that many of the electrokymographic instruments which are available to the profession today exhibit frequency responses which extend to an upper limit of only 10 cycles per second. Cardiac and vascular phenomena having a duration less than 0.1 second are therefore recorded with diminished amplitudes and with distorted configurations; furthermore, the tracings do not indicate correctly the exact time at which the phenomena take place. This is well shown in figure 1 where electrokymographic tracings made by rotating a lead sector wheel first in front of an instrument which has a frequency response extending to well over 1,000 cycles per second (curve A) and then in front of an instrument which has a frequency response extending only to 10 cycles per second (curve B) are illustrated. It will be observed that the latter instrument distorts very considerably the square wave pattern produced by the sector wheel. Furthermore, the latter instrument's tracing lags behind that of the first instrument so that the onset of the tracing incorrectly indicates the onset of the phenomenon which is being recorded by several hundredths of a second. It will be evident from figure 1 that an electrokymograph which has a frequency response that extends only to 10 cycles per second will not give satisfactory recordings of phenomena having a duration

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shorter than 0.1 second; indeed, many of longer duration will be somewhat distorted and delayed.

In addition to the poor high frequency response which has just been cited, present-day electrokymographic equipment also leaves much to be desired in its ability to record low frequency phenomena. Most of the instruments which are currently available respond poorly to frequencies below 0.5 cycles per second and consequently, are not capable of recording reliably any phenomena lasting more than 1 or 2 seconds. Densitometric phenomena which have a duration of 5 to 10 seconds therefore cannot be precisely recorded.

In an effort to overcome the inadequate frequency response and the lack of calibration in present-day electrokymographic equipment, we have developed the instrument which is illustrated in figure 2. Like all electrokymographic apparatus, the device consists of a radiation detector which is attached to the fluoroscopic screen of a roentgenoscope, an amplifier and an oscillograph.

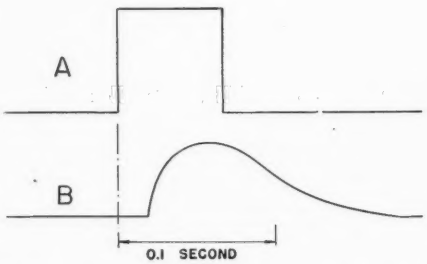

FIG. 1. Electrokymographic tracings made by rotating a lead sector wheel in front of the radiation detector of an electrokymograph. *A*. Tracings of an electrokymograph having a frequency response extending to over 1,000 cycles per second. *B*. Tracings of an electrokymograph having a frequency response extending only to 10 cycles per second.

RADIATION DETECTOR

The details of the radiation detector are shown schematically in figure 3. The unit consists of a small roentgen grid, a fluorescent screen, and the usual multiplier phototube. The roentgen grid is of a type having a 16 to 1 ratio and is employed in place of the conventional collimating diaphragms of present-day electrokymographs to prevent scattered radiation from the patient under examination from falling upon the fluorescent screen within the radiation detector. We have used a roentgen grid in this application because of its simplicity and small size.

The fluorescent screen, a zinc cadmium sulfide type (Patterson B-2), is mounted on the undersurface of a lucite block which fits snugly against the multiplier phototube. The screen size is approximately 1 cm. wide and 2 cm. long. The lucite block is so shaped that light generated within any portion of the fluorescent screen is diffused evenly over the sensitive surface of the phototube; the sensitivity of the radiation detector is thereby made uniform across its entire surface. This may be seen in figure 4 where the relative response of the electrokymograph, measured by moving a lead slit 1 mm. in width across the sensitive surface of the radiation detector, is recorded. It will be observed that when the slit encroaches upon the sensitive surface of the detector, the response rises to a maximum, remains at this level as the sensitive area is crossed and then falls to zero when the slit passes beyond.

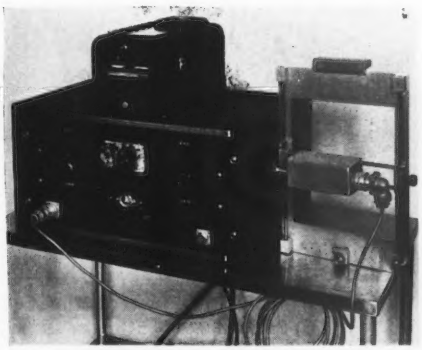

FIG. 2. The quantitative electrokymograph.

The fluorescent screen and lucite block of the radiation detector (see figure 3) are arranged so that they can be moved a distance of 5 mm. in a direction parallel to the long axis of the phototube or transversely to the incoming x-ray beam. This provision, suggested by Dr. George C. Henny of Philadelphia, has been included to provide a means for calibrating the electrokymograph when one is recording border mo-

tion phenomena. The movement of the screen and lucite block is accomplished by means of a spring-loaded button which extends beyond the end of the radiation detector and which can be pressed by the finger of the operator.

To calibrate the amplitude of a tracing, one presses the button at the end of the radiation detector and observes the amount of deflection produced on the tracing. The movement of the fluorescent screen in the amount of 5 mm. is equivalent to the movement of the structure under examination of a similar amount. At least, this is almost true and indeed would be completely true if it were not for two small discrepancies. One concerns the fact that the motion of cardiac and vascular structures is almost always accompanied by a change in the diameter of these structures; this change contributes to the amplitude of an electrokymographic tracing to some extent. The other is related to the fact that the lung fields are not uniform in density; the movement of the screen therefore may produce some deflection of the electrokymographic tracing beyond that caused by the position of the heart and great vessels. Apparently, however, these discrepancies are small in effect because calculations of cardiac and vascular motions made from electrokymographic tracings are in close agreement with measurements of these motions taken from roentgenographic films exposed in systole and diastole.

The value in millimeters of a recorded border motion is given by the equation,

$$M = A/B \times 5 \qquad (1)$$

where M is the border motion of the anatomic structure under examination, A is the electrokymographic deflection produced by that border motion and B is the electrokymographic deflection produced by moving the fluorescent screen 5 mm. A typical electrokymographic tracing made from the lower left ventricular border is shown in figure 5. It will be observed that the tracing proceeds in a regular manner until the point A is reached. At this time, the operator of the instrument pressed the calibration button of the radiation detector and the tracing became displaced upward a distance

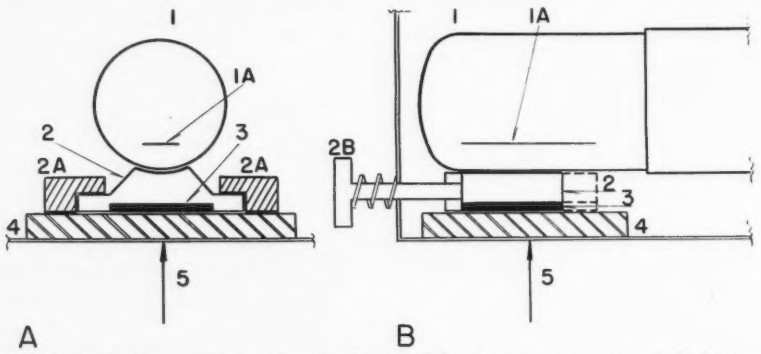

FIG. 3. Schematic diagram illustrating the details of the radiation detector. (1) Multiplier phototube. (1*A*) Sensitive surface of multiplier phototube. (2) Lucite block. (2*A*) Brackets holding lucite block. (2*B*) Spring-loaded button by which operator may move lucite block. (3) Fluorescent screen. (4) Roentgen grid. (5) X-ray beam.

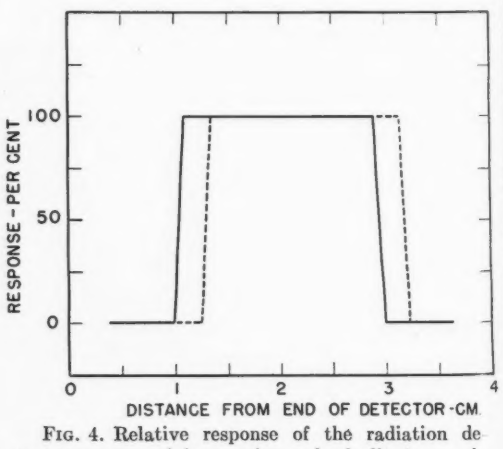

FIG. 4. Relative response of the radiation detector, measured by moving a lead slit 1 mm. in width across the sensitive surface of the instrument.

of 9 mm. Beyond point A, the tracing remains at a displaced position until point B is reached.

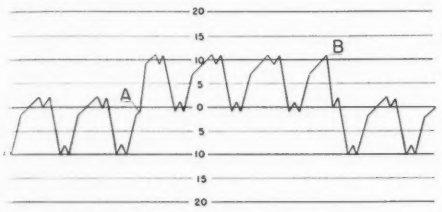

FIG. 5. Electrokymogram of lower left ventricular border illustrating the manner in which the calibration button operates.

response was poor below 1 cycle per second. In such a case, the tracing would have gradually drifted downward after its first displacement and thereby would have made the calculation of border motion very difficult.

LINEAR AMPLIFIER

A simplified circuit diagram of the amplifier with which the radiation detector operates is shown in figure 6. This amplifier is of a two stage, direct-coupled type which operates a Brush direct-writing oscillograph. The multiplier phototube, V_0, is coupled to the control

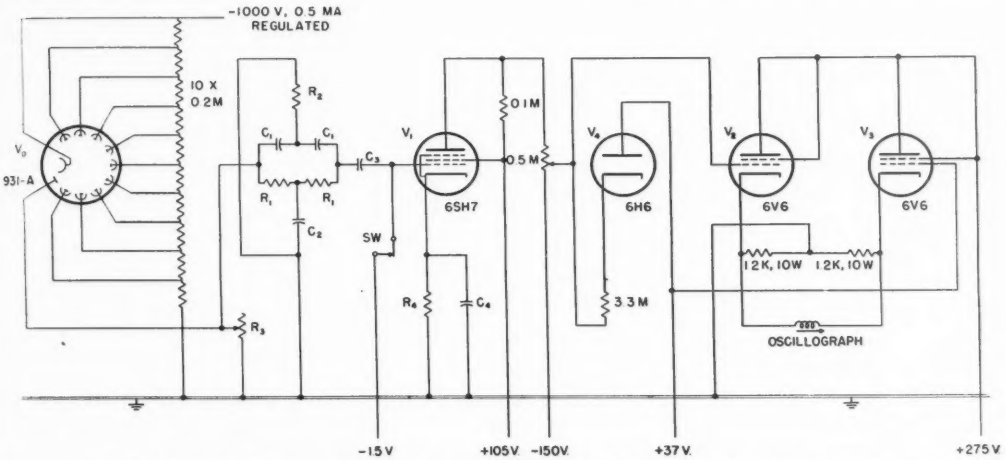

FIG. 6. Schematic diagram of linear electrokymograph. V_0, 931-A multiplier phototube; V_1, 6SH7 amplifier tube; V_2 and V_3, 6V6 power tubes; V_4, 6H6 diode; R_1, 2.7 megohm resistors; R_2, 1.35 megohm resistor; R_3, 2 megohm variable resistor; R_4, 1,000 ohm resistor; C_1, 500 $\mu\mu$f. condensers; C_2, 1,000 $\mu\mu$f. condenser; C_3, 0.05 microfarad condenser; C_4, 8 microfarad condenser.

At this time, the operator released the button of the radiation detector and the tracing returned to its original position. It will be seen that the amplitude of the tracing produced by the motion of the left ventricle is approximately 12 mm. Therefore, according to equation 1, the motion of the left ventricular border in the region where the electrokymographic tracing was taken was equal to $12/9 \times 5$ mm. or approximately 7 mm.

It will be observed in figure 5 that when the calibration button was pressed, the electrokymographic tracing remained displaced until the button was released again. This would not have been so if this type of radiation detector were used on an instrument whose frequency grid of the first amplifier tube, V_1, through the variable resistor, R_3, a parallel-T condenser-resistor filter and the condenser, C_3.

The parallel-T filter attenuates sharply the pulsations which occur within the phototube current from the sinusoidal voltage applied to the x-ray tube. Without this filter, these pulsations are sufficiently great to render the electrokymographic tracings completely uninterpretable. For a full-wave rectified fluoroscope, where maximum attenuation is needed at a frequency of 120 cycles per second, the resistors, R_1, have a value of 2.7 megohms, the resistor, R_2, a value of 1.35 megohms, the condensers, C_1, a value of 0.0005 microfarad and the condenser, C_2, a value of 0.001 microfarad. For a

self-rectified or half-wave rectified fluoroscope where the maximum attenuation is desired at 60 cycles per second, the values of the condensers, C_1 and C_2, should be double those given.

The remainder of the amplifier is relatively simple. The output of the tube, V_1, is directly coupled to a pair of 6V6 power tubes, V_2 and V_3, which in turn, are cathode coupled to the oscillograph. A 6H6 diode, V_4, is interposed between V_1 and V_2 to linearize the amplifier circuit. With this diode in place, the linearity of the amplifier is essentially uniform over the complete range of voltages needed to operate the oscillograph across its tracing paper. (See figure 7.)

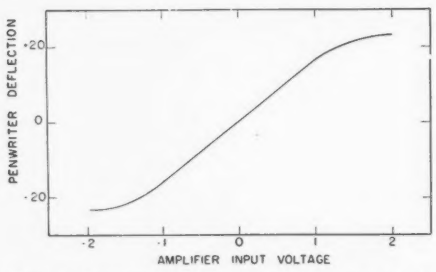

FIG. 7. Response of pen writer in terms of input voltage to the amplifier.

Although the voltages applied to the amplifier tubes are not critical, they should be maintained relatively closely within the indicated values since they have been chosen not only to assure linearity of the amplifier but also to block the amplifier should excessive signals be impressed upon it by the phototube. In this way, harm to the oscillograph by the accidental mishandling of the electrokymograph is avoided.

A. *High Frequency Response.* The presence of the parallel-T filter in the circuit impairs the high frequency response of the electrokymograph to some extent. However, this impairment has been reduced to a minimum by proper design of the filter. The value of the condensers, C_1, has been made one-half that of the condenser, C_2, and the value of the resistors, R_1, has been made double that of the resistor, R_2. Such values insure peak performance of the filter.[14] Furthermore, the value of the resistor, R_3, placed across the input of the filter has been made small and the resistance across the output of the filter has been made large relative to the value of the resistors, R_1. In fact, the resistance across the output of the filter is essentially the grid resistance of the amplifier tube, V_1, a resistance of the order of 10^{10} megohms. By this design, maximum sharpness and efficiency have been achieved for the filter.

A parallel-T filter, designed in accordance with the foregoing principles and tuned to a frequency of 120 cycles per second, exhibits some attenuation at frequencies as low as 20 cycles per second. A uniform frequency response to 40 cycles per second has been provided, however, in the electrokymograph by the inclusion of an 8 microfarad condenser, C_4, in parallel with the cathode resistor, R_4, of the tube, V_1 (see figure 6). Such a response seems sufficiently high for most electrokymographic work.

B. *Low Frequency Response.* When the radiation detector of an electrokymograph is placed over an anatomic structure and the x-ray beam turned on, the light emitted from the fluorescent screen of the detector consists of a relatively large amount of constant radiation, and a relatively small amount of fluctuating radiation which varies with the movement or density of the anatomic structure under examination. These radiations generate within the phototube large constant and small fluctuating currents respectively. Now it is the fluctuating current which one desires to record and it is necessary to remove the constant current from the electrokymographic amplifier if one is to record the fluctuating current with satisfactory amplitude. In the past, this operation has been accomplished by simple capacitative-resistive coupling between the phototube of the radiation detector and the amplifier. Although this type of coupling has been effective in producing the desired separation of the current components, it has resulted in a poor low frequency response of the electrokymograph. Furthermore, it has complicated considerably the operation of the electrokymograph by producing a great deal of instability of the instrument for 5 to 10 seconds after the x-ray beam is turned on.

The foregoing problems have been overcome in the circuit shown in figure 6 by the condenser, C_3,* and the normally closed switch, SW. These components operate in the following manner: When the x-ray beam is turned on, the condenser, C_3, charges to the voltage appearing across the input of the parallel-T filter. When the charging is complete, the switch, SW, is opened, whereupon the fluctuating potentials generated by the anatomic structure under examination are impressed upon the grid of the amplifier tube, V_1. The large constant voltage generated by the continuous light emitted by the fluorescent screen does not reach V_1 since it is exactly balanced out by the voltage which has been placed on the condenser, C_3. Now if the condenser, C_3, is given a value of 0.05 microfarad, it will become completely charged in approximately one second; thus, the electrokymograph is ready to record almost instantly after the fluoroscope is energized. Furthermore, once C_3 is charged and the switch, SW, is opened, the condenser will remain charged for a long period of time because it may discharge only through the grid impedance of the tube, V_1. Since this impedance is of the order of 10^{10} megohms, the condenser will remain charged for many seconds. Indeed, the oscillographic tracing drifts only one division in approximately 10 seconds of electrokymographic operation. Consequently, the low frequency response of the instrument is effectively uniform to frequencies approaching 0 cycles per second.

The condenser, C_3, with the aid of the switch, SW, performs three important functions: (1) it separates the fluctuating signals which one wishes to record from the constant potentials generated by the multiplier phototube from the continuous light emitted from the fluorescent screen; (2) it improves the low frequency response of the instrument so that this response extends effectively down to 0 cycles per second and (3) it simplifies the operation of the electrokymograph by stabilizing the instrument within one second after the x-ray beam is turned on. This circuit development therefore constitutes a valuable modification of electrokymographic design.

The over-all frequency response of the electrokymograph is shown in figure 8. It will be observed that the response is essentially uniform from 0 cycles per second to approximately 40 cycles per second. Measurements of the phase lag introduced by the attenuated frequency response above 40 cycles indicate that a time delay of approximately 3 milliseconds occurs between the time an event actually transpires and the time it is recorded. Such a lag seems insignificantly short.

Logarithmic Amplifier

When one wishes to record border motion phenomena, it is desirable that the electrokymograph have a response which is directly proportional to the intensity of the x-radiation transmitted by the patient. Under this condition, border motion will be recorded with greatest fidelity. When one wishes to record densitometric phenomena, however, a logarithmic response is preferable. The reason for this may be found in the following analysis.

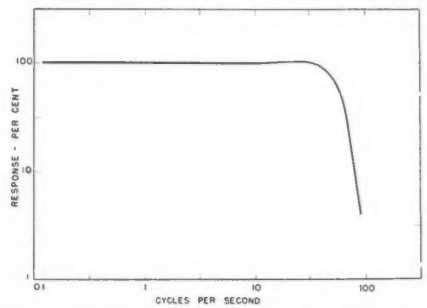

Fig. 8. Frequency response of the electrokymograph when operated as a linear instrument.

When an anatomic structure changes in thickness or density, the intensity of the x-radiation falling on the electrokymograph varies logarithmically; that is

$$\Delta \log I = B\Delta X \qquad (2)$$

where $\Delta \log I$ is the change in the logarithm of the x-ray intensity falling on the electrokymograph's radiation detector; B is a constant whose value is governed by the x-ray absorption characteristics and density of the anatomic

* This condenser must have extremely low dielectric absorption (that is, about 0.02 per cent) for satisfactory operation.

structure; and ΔX is the change in thickness of the structure. Now, if the electrokymograph has a logarithmic response, the deflection of its oscillograph may be expressed by the equation

$$\Delta D = K\Delta \log I \tag{3}$$

where ΔD is the deflection of the electrokymograph produced by the incident x-radiation, I, and K is a constant, governed by the sensitivity of the instrument. When $\Delta \log I$ is eliminated from equations 2 and 3

$$\Delta D = BK\Delta X \tag{4}$$

It will be observed from equation 4 that when the electrokymograph has a logarithmic response, the calculation of densitometric values is a simple algebraic procedure.

Because of its usefulness in the study of densitometric phenomena, a logarithmic amplifier has been included in the quantitative electrokymograph. In many respects, this amplifier, illustrated schematically in figure 9, is similar to the linear circuit shown in figure 6. Indeed, the two circuits are essentially identical, from the parallel-T filter to the oscillographic penwriter. The means by which the voltage for the multiplier phototube is provided, however, are quite different in the two instances.

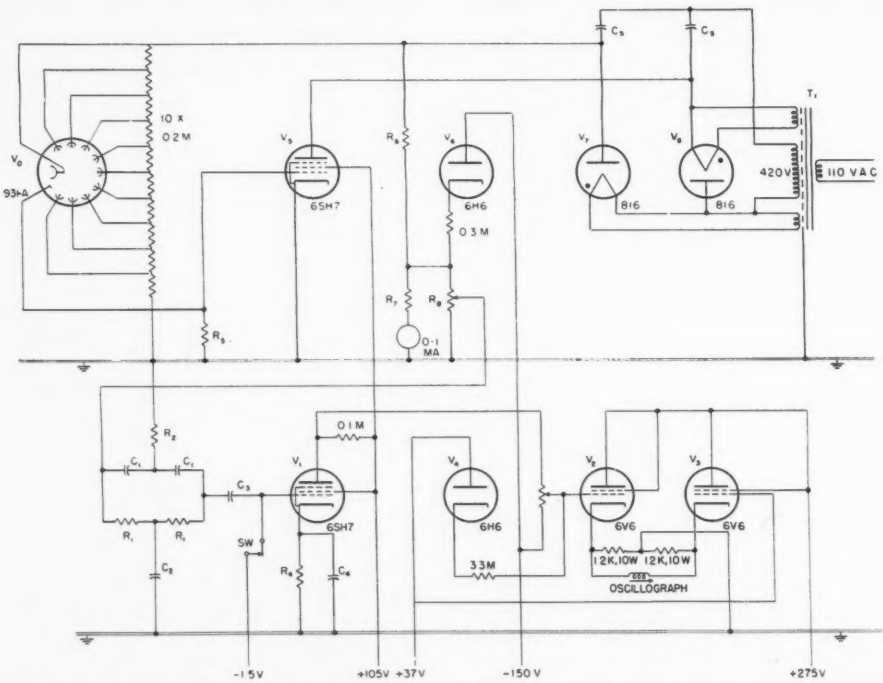

FIG. 9. Schematic diagram of logarithmic electrokymograph. V_0, 931-A multiplier phototube; V_1 and V_5, 6SH7 amplifier tubes; V_2 and V_3, 6V6 power tubes; V_4 and V_6, 6H6 double diode; V_7 and V_8, 816 rectifier tubes; T_1, power transformer; R_1, 0.27 megohm resistors; R_2, 0.135 megohm resistor; R_4, 1,000 ohm resistor; R_5, 20 megohm resistor; R_6, 0.35 megohm, 5 watt resistor; R_7, 0.18 megohm resistor; R_8, 0.18 megohm variable resistor; C_1, 0.005 microfarad condensers; C_2, 0.001 microfarad condenser; C_3, 0.5 microfarad condenser; C_4, 16 microfarad condenser.

In figure 9, the voltage developed by the transformer, T_1, the rectifier tubes, V_7 and V_8, and the condensers, C_5, is applied to the multiplier phototube through the vacuum tube, V_5. Furthermore, the output current of the phototube flows through the resistor, R_5, and the potential developed across it is impressed on the control grid of this tube. With such an arrangement, the intensity of the light incident

on the phototube's sensitive surface controls the voltage applied to the phototube's electrodes. Now the sensitivity of a multiplier phototube varies almost logarithmically with the voltage applied to its dynodes. Therefore, the voltage, appearing across the voltage divider, R_6, R_7, and R_8, bears essentially a logarithmic relationship to the intensity of the light falling on the phototube in accordance with equation 3. By means of the diode, V_6,

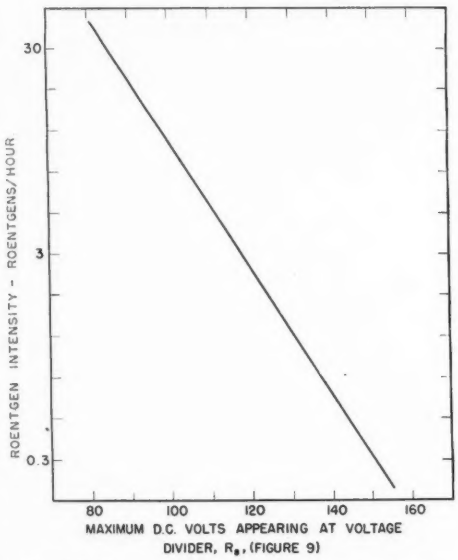

FIG. 10. Response of logarithmic amplifier as a function of the intensity of the roentgen radiation incident upon the radiation detector.

the logarithmic relationship is maintained over more than two decades of x-ray intensity. (See figure 10.)

The sensitivity of the logarithmic amplifier is controlled by the variable resistor R_8. At maximum sensitivity, the oscillographic deflection of the instrument is 500 mm. per unit change in the logarithm of the x-ray intensity; that is, K in equations 3 and 4 has a maximum value of 500. Now under normal x-ray conditions (85 kvp*) the x-ray absorption of 1 mm. of solid noncalcified biologic tissue is approximately 0.01 log unit (that is, $B = 0.01$). Therefore, according to equation 4, a change of 1 mm. in the thickness of an anatomic structure will produce a maximum deflection on the electrokymographic paper of 5 mm. Thus, the logarithmic amplifier is a quantitative instrument for densitometric studies.

The circuit illustrated in figure 9 was originally developed by Sweet[15] for photographic densitometry. Its frequency response extends only to an upper limit of approximately 20 cycles per second (curve A, fig. 11). Indeed, with a long cable connecting the amplifier and the radiation detector, the frequency response

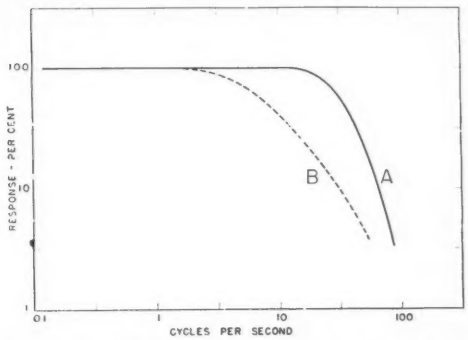

FIG. 11. Frequency response of the logarithmic amplifier. (A) Interconnecting cable 10 feet long, 20 $\mu\mu$f. per foot. (B) Cable 25 feet long, 20 $\mu\mu$f. per foot.

may not extend even to this level (curve B, fig. 11). However, since the amplifier is used only to record densitometric phenomena which take place over a relatively long period of time, such a response seems more than adequate.

DISCUSSION AND SUMMARY

The electrokymograph has been constructed so that one may obtain either a linear or logarithmic response by simply throwing a switch on the front panel of the instrument. A single channel electrocardiograph has also been included as a part of the device in order that the time relationships of the electrokymographic tracings may be easily determined within the cardiac cycle.

The operation of the instrument is extremely simple. The switch which operates the oscillograph motor has also been arranged to operate the switch, SW, of figures 6 and 9 by means of

*Kilovolts peak.

a relay. The physician therefore merely moves the radiation detector to the anatomic area he wishes to study and then sets the oscillograph in motion. Since the electrokymograph stabilizes almost instantly after the x-ray beam has been turned on, no technicians are needed to observe when the instrument is ready for recording.

In practice, the quantitative characteristics of the electrokymograph have proved quite valuable. The interpretation of many border motion phenomena have been simplified and the development of many new technics in the field of densitometric electrokymography lie before us. In the latter connection we believe it is now feasible to differentiate expansile lesions of the mediastinum from tumors of the non-expansile type with reasonable certainty.

To date, we have not evaluated the benefits that may be derived from the improved frequency response of the instrument since we have been recently interested in studying procedures for measuring rates of flow, stroke volume and residual volume of the heart by densitometric methods. There is little reason to doubt, however, that the improved response will greatly facilitate the study of many physiologic phenomena.

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CLINICAL PROGRESS

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Anticoagulant Therapy in Peripheral Vascular Disease

By NELSON W. BARKER, M.D.

DURING the past decade the anticoagulant drugs, heparin and dicumarol, have been found to be of considerable value in the treatment of many of the peripheral vascular diseases in which there is intravascular thrombosis. It is obvious that these drugs are used for the sole purpose of preventing thrombosis. To date there is no conclusive evidence to indicate that they have any effect on thrombi or emboli which have already developed. The use of both heparin and dicumarol requires careful medical supervision and involves a small calculated risk of bleeding even under the supervision of physicians who have had considerable experience with the drugs.

In various types of peripheral vascular disease the stimulus to thrombus formation varies considerably depending upon the degree of damage to the endothelium of the blood vessels, impairment of blood flow, and hypercoagulability of the blood. From a purely theoretic standpoint it seems that the only way that thrombosis can be prevented with certainty by interfering with the process of coagulation would be to make the blood totally incoagulable, a difficult and dangerous procedure if maintained for any considerable period of time. Anticoagulant therapy as carried out at present only attempts to inhibit the tendency to thrombosis by partially interfering with the coagulation mechanism. Again from the theoretic standpoint it is obvious that such anticoagulant therapy may fail if the stimulus to thrombosis is too great. However, a number of reports of experimental studies and clinical statistics indicate that, when properly given, heparin and dicumarol have prevented thrombosis in a large number of cases of peripheral vascular disease. An extensive review of anticoagulant therapy has recently been written by Marple and Wright.[1]

The statistical studies at the Mayo Clinic have indicated that among patients who have had postoperative thrombophlebitis or pulmonary emboli,[2–4] or both, the incidence of recurrence or extension of venous thrombosis and further pulmonary embolism has been reduced almost to nil by carefully supervised anticoagulant therapy. Since the tendency to thrombosis exists for only a limited period during the immediate postoperative convalescence, it is only necessary to use anticoagulants for a few weeks at the most in these cases. Furthermore, there is reasonable evidence to show that postoperative thrombosis and embolism can be almost entirely prevented if dicumarol is used prophylactically beginning 48 hours after the operation has been performed. Prior to the use of dicumarol the incidence of fatal pulmonary embolism at the Mayo Clinic after abdominal hysterectomy and after resection of the colon was 0.7 per cent. During the past nine years more than 3,000 patients who have had abdominal hysterectomy have been given dicumarol prophylactically without any instance of fatal pulmonary embolism. During the same period among the patients who underwent resection of the colon and did not receive prophylactic anticoagulant therapy, the incidence of fatal pulmonary embolism has continued to be approximately 0.7 per cent.

Wise, Loker and Brambel[5] have reported on two parallel series of patients who had undergone major surgery during a four-year period. Among 3,304 who were given dicumarol as a

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prophylactic measure, there was only one death which could possibly be due to pulmonary embolism, and among 2,030 who were not given dicumarol there were six deaths due to pulmonary embolism. To date, however, the routine use of dicumarol for the prevention of thrombosis and embolism after all operations has seemed somewhat impractical because of the statistically small risk of these complications after all operations and because of the potential danger of bleeding which also is small but cannot be ignored. However, situations are encountered, particularly among patients who have a history of previous venous thromboembolic disease, in which the risk of further thrombosis is sufficiently great to justify the prophylactic use of dicumarol following a surgical operation. In these situations it has been the practice at the Mayo Clinic in recent years to begin administration of dicumarol approximately two days after the operation and to use somewhat smaller initial doses of the drug than are employed in patients who have acute thrombophlebitis or pulmonary embolism. There have been recent reports in which it has been stated that dicumarol has been administered safely starting on the day before operation. The rationale of starting administration at this time is that therapeutic prothrombin deficiency does not develop until two or three days after the first dose of the drug has been given. For practical purposes it would seem that assuming an increased risk of bleeding by such early administration of dicumarol is unnecessary since clinically detectable venous thrombosis or pulmonary embolism rarely occurs before the sixth postoperative day. There are still variable opinions as to which surgical patients should be selected for prophylactic dicumarol postoperatively.

When postpartum thrombophlebitis or pulmonary embolism or both develop, the situation is comparable. Although information concerning sufficiently large series of treated and untreated patients is not available on which to base a statement that the use of anticoagulants has certainly reduced the incidence of further thrombosis and embolism in postpartum cases, reports of small series of cases[6] have indicated that this is probably true. A recent report by Brambel, Hunter and Fitzpatrick[7] gives the comparative incidence of thrombophlebitis and pulmonary embolism in two parallel groups of postpartum patients. Among 3,318 untreated patients there were 16 who had thromboembolic complications with one death due to embolism. Among 3,284 postpartum patients who were given dicumarol prophylactically, there were only two thromboembolic complications and no deaths due to embolism. In the untreated group, 12 had postpartum hemorrhages, and in the treated group, 17 had postpartum hemorrhages. There were no fatalities due to hemorrhage in either group. At first it was feared that the incidence and severity of postpartum hemorrhage might be greatly increased if anticoagulant drugs were given, but with proper dosage and control the risk of such hemorrhage, although it is present, appears to be very small. To date there is no evidence to indicate that nursing infants have prothrombin deficiency or bleeding while their mothers are receiving dicumarol in therapeutic amounts. Such infants are usually given synthetic vitamin K during such a period although the necessity for this is doubtful. The risk of bleeding is increased for both mother and fetus if anticoagulants are used during pregnancy, particularly in the late months.

Among patients in whom venous thromboembolic complications develop after severe injuries, such as fractures, with prolonged periods of enforced rest in bed, the situation can be closely compared to that which exists after surgery and childbirth. Experience to date does not warrant the definite conclusion that anticoagulants have prevented further thromboembolic complications, but in the experience at the clinic such recurrences have not been noted when patients so affected have been treated with anticoagulants. Because of prolonged hospitalization and rest in bed it is usually necessary to maintain anticoagulant therapy for longer periods in cases of post-traumatic thrombophlebitis and pulmonary embolism than in cases of thrombophlebitis and pulmonary embolism after operations and childbirth.

Patients who have had thrombophlebitis and pulmonary embolism in the course of acute infectious diseases have been treated successfully with anticoagulants although comparative

statistical studies concerning treated and untreated groups are not available. The rationale has been that in these cases there is a definite risk of recurrence of thrombosis and embolism similar to that noted during the postoperative period. A few instances of failure to prevent recurrent thrombosis when both heparin and dicumarol in the usual therapeutic doses have been used have been noted in patients with chronic ulcerative colitis.

It is well known that peripheral venous thrombosis and pulmonary infarction may complicate congestive heart failure and there is justification for the use of anticoagulants in all cases in which such complications develop, since they may be forerunners of more extensive and serious venous thromboembolic disease. Wishart and Chapman[8] even stated that it would be justifiable to treat all patients with congestive heart failure with dicumarol to prevent peripheral venous thrombosis. For patients with congestive heart failure, the duration of therapy is always contingent on the course of the disease, and it is hoped that the treatment can be discontinued when compensation is restored. Peripheral thromboembolic complications not infrequently develop in cases of polycythemia vera. When these complications are encountered, it is rational to use anticoagulants until the polycythemia can be brought under satisfactory control, particularly with the use of radioactive phosphorus, which seems to be an effective agent for inhibiting the tendency to thrombosis as well as controlling the erythrocytosis in this disease. The anticoagulants have been used in an attempt to prevent the recurrent venous thrombosis which has complicated inoperable carcinoma, particularly carcinoma of the pancreas. In several instances the treatment has appeared to be effective for a while but ultimately thrombosis has occurred in spite of adequate anticoagulant therapy. The incidence of failure in this group of cases has been considerably greater than in venous thromboembolic disease complicating any other type of condition.

In recurrent idiopathic thrombophlebitis (thrombophlebitis migrans), anticoagulants have been used with variable results. The irregular spacing of the episodes of activity of the disease and its variable course make it difficult to know in any individual case whether recurrences have been prevented and also how long to continue treatment. Some of these patients are somewhat resistant to anticoagulants. There have been some recurrences during treatment with dicumarol and not all of these can be explained by lapses in what is usually considered to be adequate therapeutic prothrombin deficiency. At present it seems more likely that the stimulus to thrombosis is strong and that, in some cases at least, the coagulability of the blood must be greatly impaired if thrombosis is to be prevented.

Adequate rationale and some statistical evidence are available which indicate the advisability of the use of anticoagulants in acute peripheral arterial occlusion.[4] Such cases are medical emergencies, and the success of any type of treatment is contingent on early diagnosis and early institution of therapy including anticoagulants. When the occlusion is due to arterial embolism, the source of the embolus is usually an intracardiac thrombus. There is adequate statistical evidence[9] to show that the prophylactic use of anticoagulants following acute myocardial infarction has been very effective in preventing the peripheral arterial embolisms which not infrequently complicate this type of cardiac lesion. One of the common causes of peripheral arterial embolism is thrombosis in a fibrillating left auricle. The seriousness of the prognosis for patients with auricular fibrillation who have had one or more emboli has been emphasized by many authors. Wright and Foley[10] have reported success with the prolonged use of dicumarol in the prevention of more intra-auricular thrombosis and subsequent arterial embolism in such cases.

In the specific treatment of acute arterial embolism in an extremity, heparin should be administered intravenously immediately along with measures to produce as much vasodilatation in the extremity as possible. If the circulation does not improve within a few hours and an embolectomy is considered necessary, the effect of heparin can be stopped before surgery and administration can be resumed soon after surgery. At this time dicumarol also may be given and the administration of heparin discon-

tinued as soon as the prothrombin time is adequately elevated. In the chronic occlusive arterial diseases,[11] thromboangiitis obliterans, arteriosclerosis obliterans and simple (essential) arterial thrombosis, anticoagulant therapy has not been used commonly. In thromboangiitis obliterans episodes of arterial occlusion occur usually at rather widely spaced intervals, and cessation of the use of tobacco is almost always sufficient to prevent these recurrences. In arteriosclerosis obliterans there may be episodes of acute arterial occlusion due to thrombosis in situ and during the immediate period following such episodes, anticoagulants are of value. In simple arterial thrombosis, which is a relatively rare condition, prolonged anticoagulant therapy may be advisable unless an underlying cause of the disease, such as polycythemia vera, can be brought under control.

The Use of Heparin

Heparin is a valuable anticoagulant and has the advantage of producing a rapid effect. If heparin is given intravenously, the effect can be terminated within a short time by discontinuing administration and even more quickly by administering protamine sulfate intravenously.[12] Disadvantages of heparin are its cost and difficulty of administration. Numerous studies have indicated that tolerance to heparin varies considerably among different individuals.[13, 14] Increased tolerance to heparin, manifested by less marked effect on the coagulation time after standard doses, is frequently observed among patients with various types of thrombosis. However, some such patients have normal tolerance for heparin and a few have decreased tolerance. This variability of response to fixed doses of heparin has not been sufficiently appreciated in efforts to simplify administration by standardization of dosage. The coagulation time of whole venous blood has been generally used as the guide to the anticoagulant effect of heparin.

It is not generally appreciated that this test of the blood is a very crude one and is subject to numerous errors which may impair its value greatly. The errors increase when the coagulation time is prolonged by heparin. Some of the factors which influence the results of the test are the cleanliness of the tube, the amount of blood tested, the size of the tube and the frequency and vigor with which it is tipped to determine the end point. A difficult venipuncture with considerable probing for the vein will greatly shorten the time, as compared with that after a clean, quick venipuncture. Such shortening of the coagulation time is due to the introduction of greater amounts of tissue thromboplastin into the needle. Differences in the environmental temperatures at which the tests are done may greatly affect the results. If careful attention is paid to all these factors and they are rendered as nearly constant as possible, and if the same individual does the tests, a reasonable degree of accuracy and comparability of results may be obtained. Although a number of good coagulationists have concluded that the test is subject to too many errors to be of any value whatsoever, it is the most practical test of the effect of heparin available at present.

The degree of prolongation of the coagulation time by heparin which is sufficient to inhibit intravascular thrombosis has never been definitely established but it is generally considered that it should be at least twice normal, or more than 15 minutes. Some observers have noted that even with minimal prolongation of coagulation time by heparin, the clot is softer and more friable. They have stated that this indicates that heparin may exert some antithrombotic effect when there is only slight prolongation of the coagulation time.

The method of administration of heparin first recommended by the Toronto group of investigators was to give the heparin in dilute solution, 200 mg. in 1000 cc. of diluent, continuously at a regular rate, usually starting with 25 drops per minute. The rate of administration was varied to produce the desired effect (coagulation time 15 to 25 minutes). This method was effective and individualized the dosage for each patient but it required frequent tests of the coagulation time and careful supervision of the apparatus to make sure that the desired number of drops per minute of the solution was always delivered. The method is not practical for continuous use for periods of more than 10 days.

The Swedish method of administration of

heparin, which largely supplanted the Toronto method, was to give a fixed dose of concentrated solution intravenously at stated intervals, such as 50 to 100 mg. every four to six hours. This was modified at times by increasing the dose to 150 mg. at 10:00 p.m. and omitting the 2:00 a.m. dose. Clinically this method has seemed to be effective, but it ignores entirely differences in heparin tolerance among different individuals. Also there is frequently no demonstrable effect on the coagulation time at the end of two to three hours after each injection. It is possible that the antithrombotic effect of heparin may persist for a longer period than the measurable effect on the coagulation time but there is no positive evidence of this, and it seems reasonable to assume that thrombosis is not prevented unless coagulation, as measured by this test, is impaired. Thus the intermittent intravenous injection of heparin permits frequent lapses in measurable anticoagulant effect. It has the further disadvantage of requiring many venipunctures.

The administration of heparin in a slowly absorbed medium by intramuscular or deep subcutaneous injection has gained in favor but opinion is divided as to its efficacy and safety. The biggest problem has been the determination of dosage, and there is lack of agreement regarding optimal dosage schedules, probably because differences in heparin tolerance among different patients have been ignored. The method has the advantage of simplicity, and there is no doubt but that sufficient heparin can be introduced to produce an anticoagulant effect lasting a number of hours by this route. The earlier solutions frequently produced persistent pain and occasionally considerable ecchymosis at the site of injection. More recent preparations appear to have minimized these disadvantages. If it becomes desirable to stop quickly the effect of heparin administered subcutaneously, this can be accomplished by applying an ice bag to the site of injection and by giving protamine intravenously. The dose of protamine may have to be repeated.

The degree and duration of prolongation of the coagulation time vary greatly among different patients when heparin is given intramuscularly or subcutaneously in a slowly absorbed medium. Possibly the best trial dose is 200 mg. every 12 hours but in some individuals 200 mg. produces only a minimal effect lasting less than six hours. In some individuals 200 mg. may produce an excessive effect lasting more than 12 hours. In some individuals as much as 400 or 600 mg. may be required to produce an adequate effect for 12 hours. When large doses are employed, there is always the hazard of an extreme and dangerous coagulation defect lasting as long as 12 hours after injection. Whatever initial dose is used, it is advisable to test the coagulation time one to four hours and 12 hours after administration to determine roughly the intensity and duration of effect. Results of this test then can serve as a guide to the amount and frequency of subsequent doses for the particular patient under treatment. Tolerance to heparin may fluctuate from time to time in the same patient, and to maintain an optimal anticoagulant effect it is advisable to check the coagulation time at similar intervals after the injection every few days if this type of heparin therapy is continued and to vary the amount and frequency of the dose if necessary.

Heparin produces a much more profound effect on the coagulation mechanism than does dicumarol. Even in the therapeutic range of activity there appears to be a greater tendency to bleeding from operative wounds or other potential bleeding lesions when heparin is used than when dicumarol is used. If an excessive prolongation of coagulation time is produced and maintained by heparin, the danger is obviously greater. If the hemorrhage is external and detected, the effect of the heparin can be stopped quickly, but if it is internal, a dangerous situation may develop before it is recognized.

The Use of Dicumarol

As an anticoagulant dicumarol has the advantage of being cheap and easily administered. Disadvantages are delay in adequate effect for one or more days following administration and delay of subsidence of effect for several days after administration has been discontinued. Another disadvantage which has been recognized and emphasized by all who have had experience with the drug is the great difference in response

among different patients to fixed doses. Some factors which influence this sensitivity to the drug are known and some are unknown or unpredictable. In treatment with dicumarol, the aim is to produce and maintain a moderate but not excessive deficiency of prothrombin activity. The dosage must be individualized for each patient on the basis of his reaction to certain fixed amounts of the drug which are given initially. The dosage must be varied as necessary during the entire period of administration and it depends on the response of the particular patient being treated. Nothing has developed in recent years which alters the often repeated dictum that the Quick prothrombin time test is the essential guide to dicumarol therapy and that, unless it is possible for the physician to receive accurate and comparable results of this test at daily or at even more frequent intervals if necessary, the use of dicumarol may be futile or dangerous.

In discussing "therapeutic levels" of prothrombin deficiency and dosage schedules for dicumarol, one is always handicapped by the fact that thromboplastins of variable potency are used in different laboratories and institutions for the Quick prothrombin time test. Hence, it is difficult to discuss therapy or optimal effects in terms of prothrombin time in specific numbers of seconds. An attempt has been made to discuss the optimal therapeutic range of prothrombin deficiency in terms of percentages of prothrombin activity, but this has given rise to considerable confusion because of the use of different formulas for expressing the prothrombin time in terms of percentages of prothrombin activity. For the most part it is considered that prothrombin activity between 10 per cent and 30 per cent of normal is the optimal therapeutic range when dicumarol is given. Some investigators, notably Brambel and his co-workers,[7] have concluded that for purely prophylactic purposes the therapeutic range of prothrombin activity can be 30 per cent to 50 per cent of normal.

In order to avoid confusion which exists in attempts to use percentages instead of seconds, the following scheme has been devised and can be carried out with the cooperation of any physician and any laboratory where the prothrombin time test is done regardless of the source and method of preparation of the thromboplastin. Each time a new batch of thromboplastin is prepared, T^{30}, T^{20} and T^{10} should be determined. T^{30} = average prothrombin time, in seconds, of 30 per cent plasma in 0.9 per cent sodium chloride solution from three normal persons. T^{20} = average prothrombin time, in seconds, of 20 per cent plasma in 0.9 per cent sodium chloride solution from three normal persons. T^{10} = average prothrombin time, in seconds, of 10 per cent plasma in 0.9 per cent sodium chloride solution from three normal persons.

The prothrombin time, in seconds, of the patient under treatment with dicumarol should be kept between T^{30} and T^{10}. Three hundred mg. of dicumarol are given on the first day and 100 mg. on each subsequent day that the prothrombin time is less than T^{20}. No dicumarol is given on days when the prothrombin time is greater than T^{20}. If the patient is found to be resistant to the drug, the dose is increased to 200 mg. on each day that prothrombin time is less than T^{20}. If the prothrombin time is greater than T^{10} on two successive days, 30 mg. of menadione bisulfite is given intravenously. If it is desirable to continue treatment with dicumarol for a number of weeks, a daily dose of dicumarol which will keep the prothrombin time between T^{10} and T^{30} may be determined after the first week of treatment. This dose will usually be between 50 and 100 mg. a day and the amount can be calculated roughly on the basis of whether the patient's original response to the first few doses was average, excessive or inadequate. If the patient's prothrombin time stays in the region of T^{20} or slightly higher rather consistently on the daily dose, the frequency of determinations of the prothrombin time can be gradually reduced from once a day to once a week.

Nichol[15] has suggested a somewhat simpler formula based on his observation that in a number of institutions the optimal therapeutic range of prothrombin deficiency for dicumarol therapy was expressed by a prothrombin time between two and two and one-half times normal prothrombin time in seconds. In using Nichol's formula, the normal prothrombin time should

be determined each day by taking the average of results obtained by testing two or more normal individuals who were not receiving anticoagulants. The formula, moreover, is only applicable if this normal is less than 20 seconds. Three hundred mg. of dicumarol are given the first day and 100 mg. on each subsequent day until the prothrombin time is greater than twice the established normal time in seconds for that day. Then 75 mg. are given each day if the prothrombin time is in the therapeutic range (between two and two and one-half times normal). If the prothrombin time goes above the therapeutic range, doses are omitted until it returns to the therapeutic range and then continued at the rate of 50 mg. a day. If with admistration of 75 mg. a day the prothrombin time drops below the therapeutic range, the dose is increased to 100 mg. a day. Further observation may indicate that variations in dosage by increments of 25 mg. on certain days may be necessary in some patients to keep the prothrombin time within the therapeutic range.

The contraindications to the use of dicumarol have not been changed, namely renal insufficiency, hepatic insufficiency, purpuric states and recent operation on the brain or spinal cord. In general, hypersensitivity to dicumarol may be noted among patients with congestive heart failure and patients whose nutritional status is impaired owing to inadequate diets or gastrointestinal disease. After operations, those patients who have never had evidence of thromboembolic phenomena as a group are somewhat more sensitive to dicumarol than those who have had recent thromboembolic manifestations. Dicumarol should be used somewhat more cautiously and with a somewhat reduced original dosage among patients who are considered to be potentially hypersensitive to the drug, among patients who have potentially bleeding lesions, such as ulcers of the gastrointestinal tract, open surgical wounds or granulating surfaces and among patients who have drainage tubes in wounds or body orifices.

The only important untoward effect which has been noted in patients who have received dicumarol is bleeding. Much of the serious bleeding which has been encountered has been due to gross overdosage with the drug due to error or to disregard for the importance of daily determinations of prothrombin time; however, even with adequately supervised therapy there is a small risk of serious local hemorrhage. Nichol[15] recently reviewed the cases of serious and fatal hemorrhage during administration of dicumarol in a number of institutions since the drug was first introduced. He found that the mortality attributable to hemorrhage was 0.18 per cent among 15,500 patients. A number of the fatalities occurred in the early years after dicumarol was introduced; similar situations would probably not occur now that the contraindications to the use of the drug are known more generally and the prothrombin time is determined with greater accuracy. Among patients who do not have recent surgical wounds or known ulcers of the gastrointestinal or urinary tract and present no contraindications to the use of dicumarol, the incidence of major bleeding is very low and the risk of fatal hemorrhage can be considered as practically nil providing the prothrombin time is not allowed to exceed the therapeutic range. The incidence of major bleeding, particularly bleeding from operative wounds, is higher among surgical patients in the immediate postoperative period. However, it is less than 3 per cent among those surgical patients who have not had previous thrombosis and less than 1 per cent among those who have had previous thrombosis. Among the last 2,000 postoperative patients treated with dicumarol at the Clinic no fatal hemorrhage has occurred. Wise, Loker and Brambel[5] have reported that 3,304 patients were given dicumarol after major abdominal and pelvic surgery without any deaths due to bleeding and with only three instances of bleeding sufficient to require blood transfusion. The statements in the medical literature that dicumarol is a "dangerous" drug are unjustified if the drug is properly given.

Three situations may be encountered during dicumarol therapy for which it is desirable to increase the prothrombin activity. If major bleeding is encountered, the prothrombin time should be brought down to normal as rapidly as possible. It may be advisable to stop the effect of dicumarol even when there is no bleeding if a surgical operation or some other proce-

dure involving a risk of bleeding is contemplated or when renal insufficiency develops during treatment with dicumarol. If the prothrombin time goes above the therapeutic range at any time during treatment, it is usually desirable to bring it back into the therapeutic range in order to reduce the risk of bleeding. The use of water-soluble preparations of synthetic vitamin K, such as menadione bisulfite, has been found to decrease the prothrombin which has been elevated by dicumarol in many cases. The most striking results have been noted among patients who are hypersensitive to the drug and who have excessive prothrombin deficiency after the usual initial doses of dicumarol. Several studies have indicated that vitamin K_1 and vitamin K_1 oxide given either orally or intravenously are more potent dicumarol antagonists than are the water-soluble synthetic menadione preparations. Regardless of the degree of prothrombin deficiency, the prothrombin time starts to fall within four hours and is usually normal or very near normal in 8 to 24 hours after the administration of a single dose of 500 mg. of vitamin K_1 either by mouth or by vein. Those who have used both vitamin K_1 and synthetic vitamin K seem to have no doubt but that vitamin K_1 is the preparation of choice in any situation where it is desirable to reduce the prothrombin time elevated by dicumarol to normal as rapidly as possible.[16, 17] However, when it is merely advisable to reduce an excessively elevated prothrombin time into the therapeutic range, the synthetic preparations are preferable. For practical purposes, a single dose of 500 mg. of vitamin K_1 given orally appears to be almost as rapidly and completely effective as the same dose given intravenously, except for patients who are vomiting or who have external biliary fistula or external biliary drainage. Following a single dose of 500 mg. of vitamin K_1, patients are usually refractory to the usual doses of dicumarol and similarly acting drugs for one to two weeks. Among patients who receive vitamin K_1 to stop the effect of dicumarol because of the development of renal insufficiency, the prothrombin time may become elevated again after it has returned to normal and subsequent doses of vitamin K_1 may be necessary. In almost all other cases, however, the prothrombin time remains normal after vitamin K_1 has been given. For control of excessive prothrombin deficiency due to dicumarol, transfusion of blood is of some value but is rarely necessary unless there has been major bleeding. In this situation the main purpose of transfusion is to restore lost blood rather than prothrombin. The effect of one transfusion on the prothrombin time is usually transient.

Choice of Anticoagulants and Combined Therapy

At present if anticoagulant therapy is desirable in cases of peripheral vascular disease, heparin alone should be used if the patient has definite hepatic or renal insufficiency or if adequate tests of Quick prothrombin time are not available. If such tests are available, dicumarol alone is preferable when the risk of thromboembolic complications is increased but there have been no recent acute thromboembolic complications. The preferable plan of treatment from the standpoint of effectiveness of treatment, safety and economy for patients with acute peripheral thrombosis or embolism including pulmonary embolism is the combined use of heparin and dicumarol; this statement again is based on the assumption that adequate prothrombin time tests are available and there are no contraindications to the use of dicumarol. In this plan, doses of heparin are discontinued when the prothrombin time reaches the therapeutic range, and treatment is continued with dicumarol alone. Since heparin also affects the prothrombin time, the blood samples for prothrombin time tests to determine the effect of dicumarol alone should be drawn after the effect of heparin has been allowed to lapse.

Many observers have noted that patients with acute iliofemoral thrombosis or severe pulmonary embolism have a more rapid subsidence of symptoms and manifestations if heparin is started soon after the onset.

Dicumarol is the anticoagulant of choice for long-time anticoagulant therapy because it is so much less costly than heparin.

Newer Anticoagulant Drugs

Tromexan, which is a trade name for 3,3′-carboxymethylene bis (4-hydroxycoumarin)

ethyl ester, is a new anticoagulant drug having a dicumarol-like action. Chemically it is very similar to dicumarol. This drug was developed in Switzerland and in Czechoslovakia where it is known as Pelentan. Preliminary observations on the clinical use of Tromexan have been reported by Burt, Wright and Kubik[18] in England and Burke and Wright[19] in this country. Tromexan is approximately one-fifth as potent as dicumarol milligram for milligram and therefore the dosage in milligrams is approximately five times as great. The only essential differences between the action of Tromexan and the action of dicumarol are that the effect of Tromexan develops somewhat more rapidly after administration has been started and disappears somewhat more rapidly after administration has been discontinued. Individual differences in sensitivity to Tromexan are similar to those noted with dicumarol, and when the drug is given, it is equally necessary to establish the correct dosage on the basis of daily determinations of prothrombin time. An original dose of 1200 to 1500 mg. is recommended and the usual daily dose for maintaining prothrombin deficiency in the therapeutic range is considered to be 600 to 900 mg.

It has been stated that there may be a greater safety factor in using Tromexan than in using dicumarol because of the more rapid subsidence of effect after administration of the drug has been discontinued. However, the prothrombin time of some individuals has not returned to normal for as long as four or five days after the last dose of the drug was given. In the few cases in which synthetic vitamin K has been given to patients with markedly elevated prothrombin times due to Tromexan, the return to normal seemed to be somewhat accelerated and in any event has been rather rapid (within 12 to 36 hours). The only disadvantage of Tromexan over dicumarol appears to be a somewhat greater difficulty in maintaining the prothrombin deficiency within the therapeutic range during the trial period or first week or two of administration because of the tendency to more rapid fluctuations of the prothrombin time. It is said that splitting the daily dose tends to reduce these fluctuations. To date an insufficient number of patients have been treated to determine whether the drug is as effective as dicumarol in preventing thrombosis and whether the risk of bleeding is less than when dicumarol is used. It can be anticipated, however, that if similar levels of prothrombin deficiency can be maintained, Tromexan will be equally as effective and safe as dicumarol. The more rapid development of prothrombin deficiency after the drug is given would appear to be a slight advantage in some situations.

Another drug with action similar to dicumarol which has been used recently in human beings as an anticoagulant is 4-hydroxycoumarin anticoagulant No. 63 or 2-methyl-2-methoxy-4-phenyl-5-oxodihydropyrano-(3, 2-c) (1) benzopyran. This compound was developed in the laboratory of Dr. Karl Paul Link and first reported on by Scheel, Wu and Link. It is less soluble than dicumarol and two to three times as potent milligram for milligram. Therefore, the doses recommended for producing the same levels of prothrombin deficiency are one-half to one-third those for dicumarol. It has been stated that when severe and prolonged prothrombin deficiency has been produced and maintained in animals by this drug, less tendency to bleeding has been noted than when a comparable degree and duration of prothrombin deficiency were produced by dicumarol. Clinical observations on the effects of anticoagulant No. 63 have been reported by Battle, Capps, Orth and Meyer.[20] After an original dose of the drug is given, it appears that the prothrombin deficiency develops as rapidly as or slightly more so than when dicumarol is given. Following cessation of the use of anticoagulant No. 63 the prothrombin time remains elevated for a somewhat longer period than is noted with dicumarol. In my limited experience some patients who were resistant to dicumarol developed satisfactory prothrombin deficiency when given anticoagulant No. 63 and it has seemed to be a little easier to maintain relatively constant levels of prothrombin deficiency with this drug. Rotter and Meyer have stated that synthetic vitamin K (menadione bisulfite) is ineffective in restoring the prothrombin time to normal after it has been elevated by anticoagulant No. 63 but that vitamin K_1 is just as effective as it is in patients who have received

dicumarol. To date clinical experience is inadequate for satisfactory appraisal of whether the drug has any definite superiority over dicumarol, but further trial and study seem indicated.

Another new drug which has been investigated as an anticoagulant is phenylindanedione, which also has an action like that of dicumarol on the prothrombin time. A preliminary report of the effects of administering this drug to 20 patients has been made by Blaustein and co-workers.[21] Phenylindanedione is said to have a more rapid and more evanescent action than dicumarol, both in animals and man. The effect of phenylindanedione seems to be even more evanescent than that of Tromexan. The usual initial dose which was used by Blaustein and co-workers[21] was 150 mg., and the daily maintenance dose averaged 50 mg. Interruption of sustained therapy was followed by return of the prothrombin activity to normal levels in from 48 to 72 hours. The more rapid subsidence of effect apparently increases the difficulty in maintaining the prothrombin deficiency within the so-called therapeutic limits. In some patients maintenance of relatively constant levels of prothrombin deficiency in the therapeutic range seemed to be difficult even when doses were given more frequently than once in 24 hours.

Sorenson and Wright[22] have reported studies on human beings with a polysulfuric acid ester of polyanhydromannuronic acid called Paritol. This drug has a heparin-like action and its manufacture is said to be less costly than that of heparin. Paritol acts only when it is administered intravenously, and its action consists in prolongation of the coagulation time of venous blood similar to that produced by heparin. Apparently there are differences in response to the administration of various fixed amounts of Paritol among different individuals, just as have been noted with heparin. Sorenson and Wright[22] have noted that approximately seven times as much Paritol as heparin was required to increase the coagulation time to the same degree. However, the effect of such doses lasted considerably longer, often 8 to 12 hours. A slight prolongation of the prothrombin time, similar to that produced by heparin, was noted. Of 35 patients to whom Paritol was given, one had a severe reaction with vascular collapse but recovered after administration of epinephrine; two had transient swelling of hands and feet, and one patient with renal insufficiency had a further rise in the blood urea nitrogen. Bartholomew has recently shown that the effect of Paritol can be stopped rapidly by the intravenous injection of protamine sulfate. One of Bartholomew's patients had nausea, vomiting and pains in the muscles after administration of Paritol and in a few cases, pain in ischemic extremities was aggravated without objective evidence of increased ischemia. Sorenson and Wright[22] have stated that when some of the material was injected outside the vein local pain and soreness but no necrosis developed. They concluded that the material is unsuitable for subcutaneous or intramuscular administration. The potential advantages of Paritol over heparin would seem to be its somewhat more prolonged action and possibly its decreased cost. The chief disadvantage would seem to be the uncertainty about the question of untoward reactions. Further studies of this drug regarding the toxicity would seem to be indicated before it is released for clinical use.

Some other sulfated compounds of high molecular weight are being investigated as anticoagulants having a heparin-like action.

Recently Ochsner, DeBakey and DeCamp[23] have reported on the use of a different type of anticoagulant therapy for the prevention of postoperative thrombosis and embolism. They have used alpha tocopherol (epsilan M), 200 international units orally every eight hours, or alpha tocopherol phosphate, 100 mg. intramuscularly every eight hours, and calcium gluconate, 10 cc. of a 10 per cent solution every 24 hours intravenously. This type of treatment is predicated on the observations of Kay, who found that a test for plasma antithrombin showed decreased amounts of this factor in cases in which postoperative thromboembolic complications developed. This observation lacks confirmation to date. A previous study[24] of antithrombin in the plasma of patients with thrombosis occurring in a variety of conditions showed that the antithrombin of some was less and of

some greater than in a series of normal individuals but that the mean for patients with thrombosis was the same as the mean for the normals. Ochsner and co-authors[23] have reported results in a series of 290 patients who received alpha tocopherol and calcium during the postoperative period. Apparently, presumptive venous thrombosis developed in three patients and fatal pulmonary embolism in two. That this indicates a significant reduction in occurrence of thromboembolic complications can be seriously questioned, and it seems that a much larger series of treated patients must be studied before the value of the combination of alpha tocopherol and calcium as an antithrombotic regimen can be established.

Summary

The anticoagulant drugs, heparin and dicumarol, have been of great value in the prevention and treatment of peripheral thromboembolic disease. The use of both drugs requires individualization of dosage based on the results of the appropriate tests of their effect on coagulation. The risk of bleeding is very small if heparin and dicumarol are properly used. New anticoagulant drugs are being studied and evaluated clinically in an effort to increase even further the effectiveness and safety of anticoagulant therapy.

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ABSTRACTS

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BACTERIAL ENDOCARDITIS

Stokes, J. F., Gray, J. R. and Stokes, E. J.: Actinomyces Muris Endocarditis Treated with Chloramphenicol. Brit. Heart J. **13**: 247, 1951.

A woman, age 27, with known rheumatic heart disease contracted a febrile illness one month after handling a dead rat. Blood culture was sterile. Treatment consisted of penicillin and salicylates but recovery was slow. After seven months she returned to work. Seven months later, symptoms recurred and blood cultures were positive for *Actinomyces muris*. The organism was sensitive to chloramphenicol and in one week she was symptom free. Treatment was continued for four weeks.

There were no clinical features that distinguish this infection from that usually causing subacute bacterial endocarditis. The author believes that the first episode was due to the same organism that became resistant to penicillin.

SOLOFF

Goudie, J. G., and Lowther, C. P.: Subacute Bacterial Endocarditis Due to H. Para-Influenzae and Str. Viridans. Brit. M. J. **4900**: 217 (Feb.), 1951.

The clinical and laboratory findings are given of a case of subacute bacterial endocarditis apparently due to a mixed infection with *H. para-influenzae* and *Str. viridans*. The viridans was grown only from the first blood culture but thereafter intensive penicillin therapy precluded the possibility of its subsequent isolation. The *H. para-influenzae* was grown on three separate occasions and its disappearance after antibiotic (streptomycin) therapy to which it was sensitive, accompanied by the disappearance of the pyrexia and marked clinical improvement of the patient, all point to the organism being a causal agent of the disease.

The unusually long (11 weeks) survival of *H. para-influenzae* in vitro and the method of preparing a stable suspension are thought to be interesting laboratory findings.

BERNSTEIN

CONGENITAL ANOMALIES

Selzer, A., and Laqueur, G. L.: The Eisenmenger Complex and Its Relation to the Ventricular Septum. Arch. Int. Med. **87**: 218 (Feb.), 1951.

Two new cases of the Eisenmenger complex in adults are reported in detail. In addition, data on 33 autopsied cases of this syndrome are tabulated and their clinical and pathologic features reviewed. The concept of the Eisenmenger complex is widened to include cases in which the aorta is completely dextroposed, and arises from the right ventricle.

Microscopic examination of the pulmonary arterioles in two cases revealed severe intimal and medial changes. It is believed that they constitute a characteristic feature of the Eisenmenger complex, being evidence of long-standing severe pulmonary hypertension. Further evidence is presented to support the view that no dividing line exists between the uncomplicated defect of the ventricular septum and the Eisenmenger complex, and that both are caused by varying degrees of the same process of maldevelopment. The distinguishing feature of the two syndromes, the dextroposition of the aorta, may be difficult to determine owing to the fact that in the absence of the membranous septum there is a physiologic overriding of the aorta, and that an exami-

nation of the specimen of the heart may not permit an estimate of the degree of dextroposition which existed during life. Evidence is presented that anoxemia and cyanosis are due to admixture of venous blood in the aorta, or the shunt mechanism, rather than to incomplete pulmonary oxygenation.

The hemodynamics of the Eisenmenger complex are presented in the light of recent measurements of intracardiac pressure. Four cases are included in which the triad of basal defect of the ventricular septum, dextroposition of the aorta and deformity of an aortic cusp causing aortic insufficiency existed. In contrast to the remainder of the series, in three of these cases cyanosis was absent, and in the fourth one it was questionable. It is thought that because of the associated aortic lesion the dextroposition of the aorta was nonfunctioning, and, therefore, it is suggested that these cases be classified as ventricular septal defects and not as Eisenmenger's complex associated with aortic insufficiency.

BERNSTEIN

Thompson, A. W., and Shafer, J. C.: Congenital Vascular Anomalies. J.A.M.A., **145**: 869 (March), 1951.

The clinical features of vascular anomalies would seem to depend on the stage of embryologic development at which maturation ceases. The authors have attempted to establish a classification and discuss (1) anomalies of large vessels conducting blood to the part (arterial aneurysm); (2) anomalies of large vessels conducting blood away from the part (phlebectasia); (3) anomalies of minute vessels (nevus flammeus); (4) abnormal communications between arteries and veins (arteriovenous fistula), and (5) anomalies associated with combinations of these functional elements. Methods of diagnosis are discussed. It is felt that logical therapy depends on careful diagnosis. Although surgical intervention and radiotherapy may be of value in some patients one should avoid unnecessary or useless procedures in most of these cases.

KITCHELL

Sellors, T. H., and Belcher, J. R.: Surgical Relief of Congenital Cyanotic Heart Disease. Lancet **259**: 887, 1950.

Seventy-two cases of cyanotic congenital heart disease were operated upon and followed for from six months to two and one-half years; 65 of these cases were typical instances of the tetralogy of Fallot, two had the tetralogy with situs inversus, two had transposition of the great vessels, two tricuspid atresia, two pulmonary stenosis only. Sixty-six patients had the Blalock operation, three had Pott's operation, two had pulmonary valvulotomies and one right-sided end-to-end pulmonary-subclavian anastomosis. There were nine operative deaths. Two died of arrhythmias, four of heart failure, one of thrombosis at the anastomosis, one of clotted hemothorax with mediastinal displacement and one of a cerebral thrombosis three weeks postoperatively.

The end results showed 42 patients who were markedly improved, 22 moderately improved, seven not improved, and one who died one year postoperatively from a cause which could not be determined at autopsy.

BERNSTEIN

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Facquet, J., Alhomme, P., and Corone, P.: Gas Embolism of a Coronary Artery, a Complication Following Intrauterine Injection for Artificial Abortion. Arch. d. mal. du coeur **44**: 137 (Feb.), 1951.

The authors describe electrocardiographic anomalies observed on three young women following abortion induced by injection of various materials into the uterine cavity. The changes of the electrocardiogram, consisting in inversion or flattening of T wave in limb leads and precordial leads, persisted over two to three months and terminated in complete restitution to normal. All three cases had neurologic manifestations (hemiplegia in two and protracted unconsciousness in the third), one had precordial pain and all a heart of normal size at x-ray examination. The electrocardiographic anomalies, which resembled those seen in anteroseptal infarction are ascribed by the authors to air embolism of a coronary artery following the intrauterine manipulation. To explain the "crossed" embolization, the authors quote from the literature old experiments in which it had been shown that air, injected rapidly into a peripheral vein in sufficient amount, may cross the pulmonary capillaries and appear in the greater circulation.

PICK

Mason, G. A.: Myocardial Ischemia and Its Surgical Relief. Lancet **260**: 359 (Feb.), 1951.

A series of 30 patients with severe myocardial ischemia is presented in which surgical methods for relief were attempted. Cardio-omentopexy with or without abrasion with aleuronat paste or asbestos, or pericardiotomy with abrasion and insufflation of asbestos were the usual surgical procedures. Of these, 11 did not survive the first month, three were not relieved of angina, and 16 were thought to have benefited from the grafting. Nearly all of the patients were cardiac derelicts "and to restore a third of such patients as these to full activity, even temporarily, as well as to relieve them of their pain seems to have been worthwhile."

Exact pathologic proof of the efficacy of grafting in this series is lacking but it is difficult to deny that something very striking has happened to the myocardium in the clinically successful cases. It is not unreasonable to suppose that, as in the laboratory

animal, a collateral circulation has been established. In view of the extreme degree of bilateral coronary disease likely to be present in comparable cases coming to necropsy, it is almost impossible to explain the clinical relief obtained solely by an improvement in the intercoronary circulation.

BERNSTEIN

ELECTROCARDIOGRAPHY

Somerville, W., Levine, H. D., and Thorn, G. W.: The Electrocardiogram in Addison's Disease. Medicine **30**: 43 (Feb.), 1951.

This study was based on the electrocardiograms taken on 90 patients ranging in age from 9 to 66 years with Addison's disease. Electrocardiographic studies were made at all levels of adrenal cortical function ranging from complete depletion and addisonian crisis to adequate replacement.

The electrocardiogram was normal in 48 per cent of the patients and abnormal in 52 per cent. The abnormalities in order of frequency were flat or inverted T waves, especially in left precordial leads; prolonged Q-T interval; low voltage in standard limb leads and less often in chest leads; prolonged P-R interval; increased QRS duration; and depressed RS-T segments. U waves were commonly seen, especially in patients receiving desoxycorticosterone acetate. It is believed that these U waves may be explained on the basis of increased after-potentials of cardiac muscle consequent to the lowering of serum potassium by desoxycorticosterone acetate.

In most cases desoxycorticosterone treatment resulted in no change in serial electrocardiograms despite clinical improvement. In 22 per cent, the electrocardiograms showed an increase in abnormalities. This may be due to the unmasking of latent myocardial damage by the clinical improvement and its associated increased cardiac load. In some cases it was due to lowering of serum potassium. Occasionally, in untreated cases with high serum potassium, abnormally tall T waves, depressed RS-T segments and prolonged Q-T intervals were normalized during desoxycorticosterone therapy.

There was no consistent relationship between subjective clinical state and the electrocardiogram and there was no correlation between electrocardiographic changes and increase in heart size during clinical improvement. In eight patients no distinctive electrocardiographic abnormalities occurred during addisonian crisis. Abnormal electrocardiograms were more likely when the hematocrit was low, and also when the basal metabolic rate was below −19 per cent. Almost all patients with abnormal electrocardiograms showed impaired 17-ketosteroid excretion and abnormal eosinophile response to the ACTH test.

Cortisone had no effect on the normal electrocardiograms of four patients. On the other hand, of 12 patients with abnormal tracings, cortisone resulted in improvement in the electrocardiogram in 10. The duration of cortisone effects was uncertain. The importance of depletion of carbohydrate-regulating factors in causing electrocardiographic abnormalities is suggested by these observations.

It is not yet possible to define precisely the physicochemical factors resulting in electrocardiographic abnormalities in Addison's disease. The pattern is complex and composite, and includes the following factors: deficiency of adrenocortical carbohydrate regulating factor, electrolyte imbalance, alterations in extracellular fluid volume, reduced basal metabolic rate, and anatomic changes in the myocardium. There is no specific electrocardiographic pattern of Addison's disease. The pattern in an individual case is probably the resultant of functional and structural alterations in the heart. Indeed, the latter may account for the persistence of abnormalities in certain cases despite clinical improvement.

ENSELBERG

Groedel, F. M., Miller, M., and Borchardt, P. R.: The Ventricular Complex in Direct Leads from the Auricles and Great Vessels. Exper. Med. & Surg. **9**: 48 (Feb.), 1951.

Four patients undergoing surgery of the heart or of the lungs provided the opportunity for the authors to investigate how the unipolar chest and limb leads reflect the potential variations, present at or in the heart. They found at the surface of the auricles characteristic differences in pattern of the auricular electrogram when obtained near the superior, or the inferior venae cavae, or over the rest of their surface. These three patterns were not propagated to the outer thoracic wall, where the auricular electrocardiogram consisted usually of one and the same pattern. At the surface of each ventricle, a definite pattern is present, the right and left part-electrogram. Transitional forms were found mainly near the left part-electrogram. Transitional forms were found mainly near the sulcus longitudinalis. Mixed forms were recorded over the great vessels. The right and left electrograms, with diminished voltage, were reflected on the thoracic wall, the left mainly to the left axillary line and almost the entire posterior thoracic wall, the right mainly to the midsternal area. Transitional forms, present at the cardiac surface over a small area, predominate at the chest wall in the broad area between the left axillary line and the midsternal line. Right or left cavity electrograms were not found at the surface of the heart, nor in distinct form over the shoulders. The V_R and V_L electrocardiograms were in no way identical with the ventricular initial complexes of the electrogram from the right and left auricular surface. The "two pattern theory" is valid for the initial complex of the electrograms obtained from the surface of the heart and the electrocardiograms recorded from the entire thoracic wall. The "perpendicular epicardial

projection theory" is only valid for the right and left electrogram, not for the transitional or mixed forms. The "perpendicular epicardial projection theory" is also invalid for T waves. The "perpendicular endocardial projection theory" seems to be invalid for humans, since intracavity electrocardiograms were not found at the auricular surfaces.

GELFAND

Vesell, H., and Kraemer, L. B.: Critical Rates in Ventricular Conduction. III. Simulation of Ventricular Tachycardia. Am. Heart J. **41**: 280 (Feb.) 1951.

The authors studied five patients who developed bundle branch block during paroxysms of supraventricular tachycardia (auricular fibrillation or flutter), simulating ventricular tachycardia. The impaired conduction is due to functional fatigue of a bundle branch produced when critical cardiac rates are exceeded. The differentiation between paroxysmal supraventricular tachycardia with functional fatigue block and ventricular tachycardia is important therapeutically since digitalis would be prescribed in the former only.

HELLERSTEIN

Jouve, A., Albony, M., and Lartigue, G.: A Spatial Study of the Ventricular Gradient. Arch. d. mal. du coeur **44**: 127 (Feb.), 1951.

In the majority of studies dealing with the ventricular gradient only its projection on the frontal plane has been considered. The authors present a method for the determination of its projection on a horizontal plane, with the help of precordial leads (V_2 and V_6) obtained at the level of the electrical center of the heart (point zero). The method of the determination of the latter was described by the authors in a previous communication.

By determination of the ventricular gradient in two planes it is possible to study its values in space and to verify the constants developed by Ashman. In intermediate and vertical hearts values obtained by this method were in good agreement with Ashman's criteria for normality and abnormality. Considerable deviations from the latter were found with hearts in horizontal position. The determination of the spatial ventricular gradient appears especially useful in cases in which the interpretation of its frontal projection is doubtful. This applies in instances where the anatomic axis G and A_{QRS} lie in close approximation or where ischemia of the anterior or posterior wall may produce an abnormal vectorial component, perpendicular to the frontal plane.

PICK

Liebow, I. M., and Hellerstein, H. K.: Factors Influencing the T Wave of the Electrocardiogram. III. Non-chronotrophic T Changes Produced by Acetylcholine. Am. Heart J. **41**: 266 (Feb.), 1951.

The authors studied the effects of minute doses of acetylcholine (μg.) on intracavitary, epicardial and standard leads of the electrocardiogram. Alteration of repolarization in the atria was reflected by T_A depression, and in the ventricles, by increases in the amplitude of the T wave in extracavitary leads. The expected reciprocal changes occurred in intracavitary leads. These changes were independent of any change in blood pressure and chronotropic effect of acetylcholine. The similarity of the effects of acetylcholine in these experiments and of the effect of cooling of the subendocardial lamina upon the epi-endocardial gradient of repolarization supports the concept of the influence of acetylcholine upon the deeper lamina by its effects on the Purkinje fibers.

HELLERSTEIN

Meyer, P., and Herr, R.: A Critical Study of the Electrophysiologic Value of the Ventricular Gradient. Arch. d. mal. du coeur **44**: 119 (Feb.), 1951.

The authors question the correctness of the concept of the ventricular gradient from the viewpoint of electrophysiology and of its clinical usefulness. Electromotive forces producing the T wave are more complex, asynchronous and opposite in direction than forces giving rise to the QRS. Furthermore, forces responsible for the T wave differ in magnitude from forces reflected in the electrocardiogram as R wave, the ratio being about 100/25. Simple determination of the mean electrical axis of QRS and T, used for the determination of the ventricular gradient, may omit significant anomalies of the electrocardiogram, for example, a widened S wave in right bundle branch block or anomalies of the T wave present only in the precordial leads. Since the ventricular gradient is derived from leads in a single (frontal) plane, abnormalities consisting in spatial deviations of the QRS and T vector are completely missed. Finally, it must be borne in mind that the ventricular gradient, as has been shown repeatedly, may remain within normal limits in a considerable percentage of cases with severe myocardial involvement and may be abnormal in clinically normal hearts.

PICK

McAllen, P. M.: The Electrocardiogram Associated with Low Levels of Serum Potassium. Brit. Heart J. **13**: 159, 1951.

The electrocardiograms of one individual with idiopathic steatorrhea and two with ulcerative colitis were studied in relationship to simultaneously determined blood potassiums that were below normal for a long time. Different electrocardiographic patterns were obtained with similar depressions of the blood potassiums. The electrocardiographic abnormalities consisted of (1) depressions of T waves, (2) sagging of the S-T segments, (3) increase in voltage of P waves, (4) increase in height and width of U wave,

(5) lengthening of any portion of the electrical cycle. These changes may occur singly or in any combination. Prolongation of the Q-T interval is not commonly associated with hypokalemia. Previous reports of prolongation of the Q-T interval are due to misinterpreting the broad tall U wave for a T wave.

SOLOFF

Coakley, J. B.: Congenital Absence of the Right Branch of the Bundle of His. Brit. Heart J. **13:** 148, 1951.

An instance of complete absence of the right bundle of His is reported as determined by serial microscopic study. The subject was a boy, age 19 years, who was cyanotic, on and off, since 6 years of age, who could not play normally because of fatigue. Physical examination revealed a cyanotic boy with a large heart, a systolic mitral murmur, a split mitral sound and an indeterminate type of block in the electrocardiogram. He died suddenly.

The absence of a right bundle is regarded as a congenital defect because of the clear cut healthy appearing right border of the bundle of His and of the absence of fibrous tissue.

SOLOFF

Slapak, L., and Portilla, H.: Zur Diagnostik des Hinterwandin farktes and des Hinter wandaneurysmas im Elektrokardiogramm. Acta med. Scandinav. **139:** 42, 1950.

The authors describe the electrocardiographic observations in 120 cases of posterior myocardial infarction studied by means of the limb leads, the dorsal lead of Nehb, and special derivations of these authors from the axilla and posterolateral thoracic area. Infarcts of large size produced changes in all of the leads used whereas infarcts of small size were associated with changes only in the limb leads and special leads of the authors, or the latter derivations alone. Two cases of aneurysm of areas of posterior myocardial infarctions disclosed persistent elevation of the RS-T segments in those leads showing the most striking abnormalities of infarction.

ROSENBAUM

ENDOCRINE EFFECTS ON CIRCULATION

Selye, H.: Role of the Adrenals in the Production of Renal and Cardiovascular Damage by Anterior Pituitary Preparations. Lancet **260:** 483 (March), 1951.

Under suitable experimental conditions simultaneous treatment with lyophilized anterior pituitary hormone (LAP) and cortisone causes an experimental simile of "collagen disease" or "hyalinosis" in the rat. This is characterized by an eventually fatal malignant nephrosclerosis with myocarditis (resembling that seen in acute rheumatic fever) and periarteritis nodosa. Adrenalectomy completely prevents these renal and cardiovascular lesions and enables the rats to remain physically fit despite this hormone treatment. It is concluded that the active factor in LAP exerts its principal toxic effects, and produces an experimental equivalent of "collagen disease," only in the presence of functioning adrenal tissue. Observations described elsewhere have shown that the so-called "growth hormone," or somatotrophic hormone (STH), accurately reproduces the hyalinosis syndrome caused by LAP. This effect of STH can be inhibited by cortisone, but only under conditions which permit the latter to induce marked adrenocortical atrophy. Cortisone fails to cause adrenal involution in rats treated with LAP since the latter is rich in ACTH. This agrees with the view that LAP preparation causes hyalinosis by virtue of the STH it contains and that the pathogenicity of STH depends largely upon the functional capacity of the adrenal cortex. These observations strongly support the concept according to which endogenous suprarenal hormones participate in the pathogenesis of the "collagen diseases."

BERNSTEIN

HYPERTENSION

Schroeder, H. A.: Pathogenesis of Hypertension. Am. J. Med. **10:** 189 (Feb.), 1951.

A comprehensive hypothesis concerning the pathogenesis of hypertension is presented and evaluated. Essential hypertension is felt to be initially a psychosomatic disorder in which repressed psychic disturbances produce increased activity of the sympathetic nervous system. Sympathetic stimulation may raise the blood pressure acutely, produce renal ischemia, and activate the adrenal cortex. Renal ischemia leads to the production of pressor substances and hypertension. Hypertension itself causes arteriolar sclerosis, especially in the kidney, resulting in more renal ischemia. Adrenal cortex activity itself may lead to hypertension. Variation in the degree of the causative factors (psychic and neurogenic), along with the presence and severity of the contributory factors (renal and endocrine disease as well as arteriosclerosis), account for the wide variation in the course of different patients and in the relative efficacy of various treatments. Therapy must be directed against the cause. Psychotherapy has sometimes altered the course of hypertension in the earliest stages by attempting to re-educate the individual so that he will react to his conflicts by overt action or by insight and logic, rather than resolving them by repression, emotional tension and subsequent discharge via his hypothalamus and sympathetic nervous system. The neurogenic factor may be controlled by "chemical" or operative sympathectomy. The humoral factor may be controlled by destruction of the pressor substance, inhibition of its formation, "flooding" a system with a nontoxic competitive agent, increasing the concentration of a

naturally occurring antagonist, and increasing renal blood flow by nonspecific methods.

HARRIS

Goetz, R. H.: The Effect of Sympathicolytic Drugs on the Cardiovascular System in Man with Special Reference to Hypertension. Angiology **2:** 1 (Feb.), 1951.

The author reviews his own experiences and those of others in the clinical use of sympathicolytic drugs. The current status of these agents is summarized. Dehydroergocornine is of more value in the treatment of hypertension than of peripheral vascular diseases. Tetraethylammonium chloride is of value in relieving causalgic pain. The marked postural hypotensive effect of the polymethylene-bistrimethylammonium compounds (C5 and C6) mitigates against their therapeutic usefulness. Priscol represents the most easily administered sympathicolytic drug at present available. It is effective orally, intramuscularly, and intravenously and in cases of spastic vascular disease has produced, on oral administration effects equal to the effect of sympathectomy. Both Dibenamine and benzodioxane are of value in the diagnosis and management of pheochromocytoma.

WESSLER

Selye, H.: Role of Somatotrophic Hormone in the Production of Malignant Nephrosclerosis, Periarteritis Nodosa, and Hypertensive Disease. Brit. Med. J. 4701: 263 (Feb.), 1951.

Experiments on female piebald rats revealed that electrophoretically pure somatotrophic hormone (STH) produces nephrosclerosis with variable degrees of nephritis, marked polyuria, myocarditis, pancreatic periarteritis nodosa, and hypertension. The type of the toxic manifestations, as well as the sensitization of the animals to these STH effects by unilateral nephrectomy and NaCl, parallel previous findings in animals receiving excesses of desoxycorticosterone acetate (DCA) or lyophilized anterior pituitary (LAP) material.

It is assumed that STH is the active principle responsible for the toxic actions of LAP upon the kidney and the cardiovascular system. The lesions caused by STH are considered to be, in all likelihood, secondary to a sensitization of the tissues to DCA-like mineralocorticoids. In addition, STH may also increase the production of mineralocorticoids by the adrenals.

The cardiovascular and renal damage normally caused by STH overdosage is prevented if cortisone is simultaneously administered in doses adequate to produce adrenocortical atrophy. In the production of the so-called "diseases of adaptation" STH appears to play a part equally as important as that of ACTH. The former is responsible for the activity of mineralocorticoids, which stimulate defensive granuloma formation, while the latter regulates the secretion of glucocorticoids, which inhibit such defense reactions.

BERNSTEIN

Elkins, C. W., and Rack, F. J.: Cerebral Pseudotumor or Intracranial Hypertension of Unknown Cause. New England J. Med. **244:** 171 (Feb.), 1951.

Three cases are described in which there was persistent or intermittent increased intracranial pressure without demonstrable cause. The signs and symptoms were similar and referable to increased intracranial pressure. They included severe headache, lethargy, blurring of vision, vomiting and palpilledema. The spinal fluid pressures were greatly elevated but the spinal fluid was normal. Ventriculograms disclosed no abnormalities. Postmortem examination disclosed no abnormalities in one patient who died after exploratory procedures upon the brain. A second patient recovered when treated by simple decompression and a third had repeated attacks over a period of seven years despite three decompressions. The authors refer to nearly forty similar cases which have been recorded in the literature. Dandy is said to have defined the syndrome as the signs and symptoms of a space-occupying lesion that could not be demonstrated.

ROSENBAUM

Tosteson, D. C., Defriez, A. I. C., Abrams, M., Gottschalk, C. W., and Landis, E. M.: Effects of Adrenalectomy, Desoxycorticosterone Acetate and Increased Fluid Intake on Intake of Sodium Chloride and Bicarbonate by Hypertensive and Normal Rats. Am. J. Physiol. **164:** 369 (Feb.), 1951.

It has been previously demonstrated that hypertensive rats, when given a free choice, ingest much less sodium chloride and sodium bicarbonate than do normal rats. Adrenalectomy and DCA increased the intake of 0.17 M sodium chloride in both normal and hypertensive rats made hypertensive by latex encapsulation. The increases were less, however, in sodium chloride selected by normal rats. Reduced intake of sodium chloride by hypertensive rats is independent of adrenal glands or increased water intake. The authors suggest altered renal function as a possible cause of reduced sodium chloride uptake in hypertensive rats.

OPPENHEIMER

McElin, T. W., Faber, J. E., and Randall, L. M.: True Toxemia of Pregnancy Occurring before the Third Trimester; Report of Three Cases and Review of the Literature. Am. J. Obst. & Gynec. **61:** 379 (Feb.), 1951.

Detailed summaries of three patients manifesting symptoms of toxemia of pregnancy prior to the third trimester of their respective pregnancies are pre-

sented. Two of the patients were primigravid, the other was gravida 1, para 0. Two had been found normal with respect to blood pressure readings and urinalyses during the initial examinations at the time of pregnancy. Pregnancy was terminated in each of these patients by hysterotomy because of a progressively deteriorating course despite vigorous therapy. Postoperative recovery was satisfactory with an improvement in the urinary findings, blood pressure and retinopathy in each instance. The authors have reviewed the literature and emphasize that true toxemia of pregnancy may occur prior to the third trimester. The presence of cardiovascular or renal disease antedating the pregnancy should be excluded and the diagnosis substantiated by the rapid clearing of symptoms with the termination of pregnancy.

SHUMAN

Calkins, E., Dana, G. W., and Howard, J. E.: Current Methods of Diagnosis of Pheochromocytoma. J.A.M.A. **145:** 880 (March), 1951.

The series of reported proved cases of pheochromocytoma now reaches over 100 with a variety of clinical patterns being recognized. Of the pharmacologic tests the authors feel the most reliable agent is histamine. Rapid intravenous injection of between 0.05 and 0.0125 mg. of histamine base was invariably followed by a severe flush, headache and a sharp but fleeting fall in blood pressure. In five of the six cases subsequently proved to be pheochromocytoma the patients, after injection, suddenly blanched and cried in alarm and the blood pressure rose precipitously. The patients broke out in profuse sweats, the pupils dilated, and all the manifestations of a severe spontaneous attack were experienced. One case studied by the authors failed to give a positive histamine test, but on exploratory surgery pheochromocytoma was found. Subsequent events showed that there was little doubt her paroxysmal hypertension was caused by this tumor. Benzodioxan test was positive in one patient in the series and negative in two other patients who had proved pheochromocytoma. The authors state although roentgenograms following perirenal air injection have been reported to be effective, interpretation in their cases was often confusing. In one instance alarming though not fatal air embolism occurred. In their later cases laminograms have been used and correctly localized the tumor in three cases. While tests may be extremely helpful no one of them can be interpreted as absolute evidence and the clinical picture must be regarded as a whole. Where reasonable doubt occurs abdominal exploration should be performed.

KITCHELL

Pantridge, J. F., and Burrows, M. McC.: A Case of Adrenal Phaeochromocytoma. Brit. Med. J.: 4704 448 (March), 1951.

The successful removal of a pheochromocytoma from a 66 year old female is reported. The test substances, histamine and acetyl-β-methylcholine, failed to produce a typical paroxysm. The rise in blood pressure after injection of these substances and that following abdominal palpation were not associated with tachycardia, nor with any of the symptoms or other signs which characterize a spontaneously occurring attack. The pressor effect of noradrenaline following intravenous injection is not usually associated with tachycardia or with distressing subjective symptoms. It might, therefore, be postulated that asymptomatic paroxysmal hypertension in the presence of pheochromocytoma is due to the release of noradrenaline and that attacks with tachycardia and marked subjective symptoms follow the release of adrenaline. The value of noradrenaline in the control of postoperative hypotension is again noted.

BERNSTEIN

Crowther, K. V.: Two Cases of Phaeochromocytoma. Lancet **260:** 445, (March) 1951.

Two cases of pheochromocytoma are described. In the first, as a result of radiologic investigation, a malformed kidney was thought to be the cause of hypertension. An unsuspected pheochromocytoma was present however, and death occurred shortly after operation.

In the second case the diagnosis was made clinically and was confirmed by the Goldenberg test, using piperoxane. Calcification in the tumor was demonstrated by radiography. The blood pressure was recorded at frequent intervals during the operation for removal of the tumor in the second case and was controlled by piperoxane and adrenaline as indicated.

BERNSTEIN

Swan, H. J. C.: Phaeochromocytoma of Adrenal Gland, with Sustained Hypertension. Brit. Med. J. 4704: 440, (March) 1951.

A case of pheochromocytoma of the left adrenal gland in which the tumor was successfully removed is described. The arterial blood pressure, which had been persistently elevated for at least seven years, reverted to normal levels. The preoperative diagnosis was essential hypertension and a splanchnic sympathectomy was decided upon. At surgery, a tumor was found in the left adrenal gland and was successfully removed. The postoperative collapse which supervened was overcome by an infusion of *l*-noradrenaline. In retrospect certain clinical features such as excessive sweating, low grade pyrexia, peripheral vasomotor phenomena, and episodes of pallor were noted which should have suggested the postoperative diagnosis.

BERNSTEIN

PATHOLOGIC PHYSIOLOGY

Adlersberg, D., Schaefer, L., and Drachman, S. T.: Development of Hypercholesteremia during Cortisone and ACTH Therapy. J. A. M. A. **144:** 909 (Nov.), 1950.

The authors discuss the development of hypercholesteremia during cortisone and pituitary adrenocorticotropic hormone (ACTH) therapy. Hypercholesteremia in man has thus far been produced by only one hormonal mechanism, that is, the suppression of normal thyroid function. The present study shows that a second hormonal mechanism now becomes available to researchers with the demonstration that prolonged administration of cortisone or pituitary adrenocorticotropic hormone can produce abnormal cholesterol elevations. The impression was that cortisone produced a somewhat higher or more sustained level of serum cholesterol for the following reasons: (1) Cortisone given after ACTH showed a definite additional elevation in the cholesterol values even though the first drug had already produced hypercholesteremia. Conversely, when ACTH was given following cortisone, there frequently was a fall in the serum cholesterol, at times below hypercholesteremic levels. (2) At times the serum cholesterol level fluctuated above and below hypercholesteremic levels. This occurred on five occasions during ACTH therapy and only once during cortisone therapy. The study revealed that patients on prolonged cortisone therapy displayed more sustained cholesterol elevation than did those on ACTH. The authors discussed the production of many of the signs, symptoms and laboratory indications of Cushing's syndrome in patients who have received prolonged courses of cortisone or ACTH, and the possible development of premature atherosclerosis in these persons, perhaps related to the sustained hypercholesteremia.

KITCHELL

Gorlin, I. R., and Gorlin, S. G.: Hydraulic Formula for Calculation of the Area of the Stenotic Mitral Valve, Other Cardiac Valves, and Central Circulatory Shunts. I. Am. Heart J. **41:** 1 (Jan.), 1951.

The authors have applied the hydraulic principles and formulas of fixed orifices to the in vivo estimation of degrees of valvular stenosis. These formulas were considered applicable because of the high kinetic energy loss through small fixed orifices or in the presence of high volume flow. In its general form, the formula is $A = \frac{F}{C\sqrt{2\,gh}}$. A is the cross sectional area in sq. cm. of orifice; F is the rate of blood flow in cc. during the time the valve or orifice is open; h is the "loss of head" or the pressure gradient across the valve or orifice; C is an empiric constant which consists of corrections for the conversion of pressure in mm. Hg to cm. and, in the case of the mitral valve, a correction for the method used of estimating the diastolic filling period; and g is gravity acceleration. To confirm the applicability of this formula to the living patient, a fresh autopsy specimen of a stenotic mitral valve was set up in an artificial pressure and flow system. Readings at all levels of pressure checked closely with calculated values. Calculated and measured areas of stenotic mitral valves checked within 0.2 sq. cm. in six postmortem examinations and in 5 patients at the time of operation. Changes in mitral valve area following fracture valvuloplasty were noted in 2 patients.

Formulas have likewise been derived for the calculation of the cross sectional area of stenotic pulmonic, tricuspid and aortic valves, patent ductus arteriosus and of atrial and ventricular septal defects. These formulas are valuable (1) in the objective appraisal of operative procedures designed to widen stenotic orifices or to abolish abnormal shunts; (2) selection of patients with sufficient stenosis to account for their major symptoms (in mitral stenosis, valve area of less than 1.5 sq. cm.); (3) to determine the size of the valve orifice that must be created at operation in order to relieve symptoms. These formulas cannot be applied to normal valves since the pressure gradient across the normal valve cannot be measured.

HELLERSTEIN

Asteroth, H., and Kreuziger, H.: Studies on the Distensibility of the Carotid Sinus in Deceased Normotensives and Hypertensives. Ztschr. f. Kreislaufforsch. **40:** 11 (Jan.), 1951.

The authors measured, with help of a specially constructed device, the distensibility of the carotid sinus and adjacent parts of the carotid arteries excised from bodies of normotensives and of patients who had during life various types of hypertension. The results were then correlated with clinical data. A definite parallel was found between the impairment of elasticity of the excised vessel on one hand, and the age and the degree of hypertension on the other hand. The correlation was especially striking among females. A marked loss of distensibility was present in cases of essential hypertension and was most marked in patients who died of malignant sclerosis. Cases of chronic nephritis failed to reveal alterations of elasticity of the vascular wall if compared with normotonics of corresponding age groups.

PICK

Mendlowitz, M., Touroff, A. S. W., and Abel, H. A.: The Effect of Venous and Arterial Occlusion, and Sympathetic Nerve Tone, on Digital Blood Flow. J. Clin. Investigation **30:** 94 (Jan.), 1951.

The blood flow through digits was measured calorimetrically in man after arterial and after venous obstruction, using heat supplemented by tetraethylammonium chloride (TEAC) to release

sympathetic tone. In addition blood flow measurements were performed during spinal anesthesia.

In this experiment spinal anesthesia produced no greater release of sympathetic tone in a toe than indirect heat supplemented with tetraethylammonium chloride as measured by skin temperatures. There was evidence that prolonged venous obstruction is incomplete because of considerable reflux through deep veins. The authors also discuss the several factors which are responsible for discrepancies between plethysmographic and calorimetric data.

WAIFE

Shenkin, H. A., Gabieses, F., and van den Noordt, G.: The Effect of Bilateral Stellectomy upon the Cerebral Circulation of Man. J. Clin. Investigation **30:** 90 (Jan.), 1951.

To study the role of the sympathetic system in the cerebral circulation, blood flow measurements were made before and after bilateral stellate ganglionectomy in 7 patients. Four subjects had Parkinson's disease, and one each had advanced cerebral arteriosclerosis, hypertension with cerebral atrophy, and old hemiplegia.

Using the nitrous oxide method a significant decrease in cerebrovascular resistance was noted after stellate ganglionectomy. The cerebral blood flow was increased to a moderate extent. A high correlation was found between the preoperative cerebral blood flow and the decrease in cerebral vascular resistance. Stellectomy reduced the vascular resistance particularly in patients with abnormally slow blood flows and increased resistance. This may indicate that a portion of the increased resistance can be due to spasm mediated over sympathetic reflexes.

WAIFE

Gorlin, R., Haynes, F. W., Goodale, W. T., Sawyer, C. G., Dow, J. W., and Dexter, L.: Studies of the Circulatory Dynamics in Mitral Stenosis. II. Altered Dynamics at Rest. Am. Heart J. **41:** 30 (Jan.), 1951.

The authors have described the deviations from the normal circulatory pattern in 21 patients with mitral stenosis studied by cardiac catheterization. They have related the physiologic responses and clinical symptoms to the severity of the mitral stenosis and to the magnitude of the pulmonary vascular changes. The mitral valve orifice areas were calculated from standard hydrokinetic orifice formulas. There was a good correlation between the clinical classification of patients and the calculated mitral valve orifice area. In Class IV patients the areas were less than 1.0 sq. cm., and in Classes I and II, more than 1.5 sq. cm. There was an increase of tissue oxygen extraction (as measured by arteriovenous oxygen difference), pulmonary artery, pulmonary "capillary" and right atrial mean pressures, pulmonary arteriolar resistance, total pulmonary resistance, and right ventricular pressure work. Cardiac output, cardiac index, and stroke volume were decreased, although there was a wide range of values. Patients with auricular fibrillation had lower cardiac indexes than those with normal sinus rhythm and similar pulse rates, supporting the concept that atrial systole contributes a significant portion of the left ventricular inflow. Pulmonary "capillary" pressures were increased above normal as a result of the increase in left atrial pressure proximal to the stenotic mitral valve. Six patients had pulmonary edema during the study. Each had pulmonary capillary pressures in excess of 30 mm. Hg. Pulmonary arterial pressure was increased as a result of the rise of pulmonary capillary pressure and increased pulmonary arteriolar resistance. The latter was due to true pulmonary parenchymal or vascular disease. The work of the right ventricle against pressure was increased from two to four times the normal. Inadequacy of the right ventricle, as indicated by an elevated filling pressure, was seen in over one-half of the patients. Incompetence was believed to be due to increased pulmonary pressure load and underlying myocardial damage from rheumatic fever. On the other hand, paroxysmal pulmonary edema develops in patients with overactive competent right ventricles. A momentary increase in right ventricular output over the left produces an increase of pulmonary blood volume and pulmonary capillary pressure, and therewith pulmonary edema.

HELLERSTEIN

Penrod, K. E.: Cardiac Oxygenation during Severe Hypothermia in Dog. Am. J. Physiol. **164:** 79 (Jan.), 1951.

Coronary arteriovenous oxygen differences were normal at 20 C. heart blood temperature. Although the hemoglobin dissociation was shifted to the left, no serious hypoxia resulted. Breathing 100 per cent oxygen does not affect the coronary arteriovenous difference. Coronary venous oxygen pressure values of 4 to 5 mm. Hg often occur at 20 C. blood temperature with no evidence of impaired oxygenation of heart muscle. It is concluded that cardiac muscle has a striking ability to extract oxygen from blood at very low pressures.

OPPENHEIMER

Mufson, I.: Responses of the Abnormal Arterial Circulation to Various Stimuli, as Studied by the Use of Radioactive Sodium. II. Intraarterial Histamine, Papaverine, Aminophylline and Adrenaline; Sympathectomy and Etamon; Pain. Ann. Int. Med. **34:** 428 (Feb.), 1951.

As a result of measurements of radiosodium diffusion through the peripheral vascular system, the effectiveness of histamine and of sympathetic block as vasodilators in obliterative arterial diseases was demonstrated. By this technic, intraarterial papaverine, aminophylline, and intravenous Etamon were

found to be ineffective where histamine intra-arterially was effective as a vasodilator. The difference in the effects which have been produced by histamine intraarterially and by paravertebral nerve block when a limb was edematous because of a deep venous thrombus and lymphedema, has suggested the possibility that the effect of histamine is mainly on the minute vessels and capillaries while that of sympathetic block is on the arteriovenous anastamoses.

WENDKOS

Nylin, G.: Studies of Changes of the Amount of Residual Blood of the Heart in Man. Cardiologia **17:** 251, 1950.

The author discusses results of an attempt to calculate the amount of rest volume of the heart in normal subjects and under pathologic conditions. The method consisted in a correlation of the heart volume, calculated from roentgenograms taken in two planes, with the circulation time. Circulation time was determined by following the curve of concentration in the arterial and venous blood of erythrocytes labeled with radioactive P^{32} and injected intravenously.

Even in the healthy subjects there is probably a small amount of residual blood. In pathologic conditions it varies greatly corresponding to the degree of dilatation of the heart and the form of the dilution curve of the labeled erythrocytes. Calculations of the amount of "pool blood" from this curve may not be valid due to the impossibility of determining exactly the time when recirculation begins.

PICK

PATHOLOGY

Pariscenti, P.: Observations of the Heart in Hemochromatosis. Folia cardiol. **9:** 345 (Aug.), 1950.

A case of hemochromatosis with cardiac involvement is studied in detail. Thirty-five cases of hemochromatosis found in the literature are reviewed. The opinion of the author is that myocardial involvement is quite frequent in this disease and is a potential condition of failure. This possibility should be taken into consideration even when the electrocardiographic findings are negative. The failure which occurs in this disease can be chronic, acute or subacute. It cannot be controlled clinically because of the irreversible type of lesion of the myocardial fibers. The nature of these lesions is still obscure.

LUISADA

Littler, T. R., and Canter, S.: Acrosclerosis. Lancet **260:** 139 (Jan.), 1951.

Acrosclerosis is relatively rare, and there is much conflict of opinion about whether it is an independent clinical syndrome or not. Acrosclerosis, scleroderma, scleroderma adultorum, and dermatomyositis have all been grouped together as dermatosclerosis because hardening of the skin is common to all of them at some time during their course. The cardinal feature of acrosclerosis is its invariable association with the Raynaud phenomenon; this is usually well established months or years before the skin lesions appear, but occasionally the vasomotor and cutaneous signs appear almost simultaneously. The characteristic features are outlined and differential diagnosis discussed. Most important besides the vasomotor phenomena is the fact that the process is always confined to the extremities and the face.

Etiology is discussed in general with special reference to the adrenal glands. It is suggested that these glands may ultimately be directly concerned in the pathogenesis of acrosclerosis. Treatment, both medical and surgical, is briefly discussed.

BERNSTEIN

Hyman, A. L., Levy, L., II, Bagnetto, R., Ordway, N. K., and Hull, E.: Isolated Disease of the Pulmonary Valve and Artery. Ann. Int. Med. **34:** 90 (Jan.), 1951.

Seven representative cases of isolated disease of the pulmonary valve or artery are reported. The first 3 cases are examples of congenital pulmonary stenosis, 2 of which were due to involvement of the valve itself and one to involvement of the infundibulum of the right ventricle. In the single case of infundibular pulmonary stenosis, the diagnosis was made during life because of findings similar to those observed in the cases of valvular stenosis except for the absence of a prominent pulmonary conus and right heart failure. In the case of the infant, the lesion was demonstrated at autopsy. Final confirmation of the diagnosis in the older child with pulmonic valvular stenosis and in the child with infundibular stenosis was obtained from angiocardiograms and catheterization studies which showed a high right ventricular pressure and a low pulmonary artery pressure in conjunction with normal arterial oxygen values. The fourth case is that of a subacute bacterial endocarditis limited to the pulmonic valve, the diagnosis having been established during life only when a blood sample, removed from the pulmonary artery during catheterization of the right ventricle, yielded a nonhemolytic streptococcus when cultured. Recovery followed the institution of intensive penicillin therapy after the positive blood culture was obtained. During the height of the illness, systolic and diastolic murmurs of variable intensity were audible over the pulmonic valve area. The fifth case is one of suspected rheumatic pulmonic valvulitis although the basis for this diagnosis is somewhat questionable. The last 2 cases are examples of pulmonary artery aneurysms due to intrinsic disease of the vessel wall, one the result of syphilitic and the other of tuberculous involvement. In both cases, angiocardiograms helped to establish the diagnosis and ruled out aortic aneurysm.

WENDKOS

Lindeboom, G. A., and Westerveld-Brandon E. R.: Dilatation of the Aorta in Arachnodactyly. Cardiologia **17:** 217, 1950.

Of 13 patients with arachnodactyly (Marfan's disease), 5 showed an aortic lesion. This consisted of dilatation of the ascending aorta or of the beginning of the descending aorta. In another patient there was a suggestion of a congenital weakness of the external carotid artery wall. In view of the several cases of fatal dissecting aneurysm in arachnodactyly the authors suggest that more attention be paid to the aorta and the large vessels in this syndrome.

WAIFE

PHARMACOLOGY

Heymans, C., and Van Den Heuvel, G.: Action of Drugs on Arterial Wall of Carotid Sinus and Blood Pressure. Arch. internat. de pharmacodyn. et de thérap. **83:** 520 (Sept.), 1950.

The authors studied the effects of certain drugs acting on the carotid sinus by cutting the vagus and aortic nerves of anesthetized dogs. Clamping the carotid arteries induced a marked reflex rise in systemic pressure with return to normal on declamping. Infiltration of the carotid sinus areas with 1 per cent *l*-adrenaline led to a progressive and prolonged fall in blood pressure, at which level carotid artery occlusion had no effect on blood pressure. *l*-Noradrenaline and pitressin applied locally to the carotid sinus areas caused a contraction of the arterial wall and stimulated the receptors of the carotid sinus nerves which reflexly buffer the arterial pressure. Such a stimulation of the pressoreceptors led to a marked and prolonged fall in arterial pressure. These substances also induced a suppression of reflexes normally provoked by a decrease in pressure inside the carotid sinus area (clamping).

Section of the carotid sinus nerves after this fall in pressure caused an immediate and very marked rise in systemic arterial pressure.

Papaverine and Priscol applied similarly caused a rise in systemic pressure through a decrease in stimulation of the pressoreceptors.

WAIFE

Bell, G. O., and Mishtowt, G. I.: Use and Abuse of Thiouracil Drugs. Am. J. Med. **10:** 68 (Jan.), 1951.

The authors appraise the current status of the preoperative and long term use of thiouracil derivatives. Propylthiouracil is the drug of choice. Methylthiouracil, although more active, is more toxic. Thiouracil has been recommended in the treatment of thyroiditis. The commonest abuses include failure to control the hyperthyroidism completely due to inadequate dosage; improper selection of cases for prolonged medical treatment, such as intrathoracic goiters, very large adenomatous goiters, or large exophthalmic goiters; mistaken diagnosis; and the use of small doses which accomplish little, but expose the patient to possible drug sensitivity. Toxic reactions to propylthiouracil occur in 2 per cent of patients. In 0.6 per cent of patients agranulocytosis may develop. The type of hyperthyroidism most likely to respond to medical treatment is primary hyperthyroidism or Graves' disease with small glands and mild toxicity.

HARRIS

Siedeck, H., and Tomek, S.: Digitalis Therapy in Chronic Heart Failure. Cardiologia **17:** 334, 1950.

The authors compared the effect of strophanthin K, lanatoside C (Cedilanid) and digitoxin on the cardiodynamics in 32 cases with various types of heart failure using the method of Schultz and Blumberger for the determination of the phases of isometric contraction and of ejection. In cases of hypertensive and/or arteriosclerotic heart disease and cases with aortic lesions, strophanthin and Cedilanid proved most effective by shortening the isometric contraction and lengthening the ejection time. Similar and optimal results were obtained in mitral and tricuspid lesions with digitoxin. All three glycosides had but little effect on the failing cor pulmonale.

PICK

Werko, L., and Lagerlof, H.: Studies on the Circulation of Blood in Man. VII. The Effect of a Single Intravenous Dose of Theophylline Diethanolamine on Cardiac Output, Pulmonary Blood Volume, and Systemic and Pulmonary Blood Pressures in Hypertensive Cardiovascular Disease. Scand. J. Clin. & Lab. Investigation **2:** 181, 1950.

Changes following 0.4 Gm. doses of theophylline diethanolamine were observed in 11 patients. Cardiac output rose slightly in the compensated cases, parallel with a rise in oxygen consumption. In the decompensated cases cardiac output rose more than the oxygen consumption, resulting in decreased arteriovenous oxygen difference and a better metabolic oxygen exchange. The data imply that the drug has a direct myocardial stimulating action. Both systemic and pulmonary venous pressures were rapidly lowered, presumably due to dilatation of the vascular bed. Pulmonary arterial blood pressures were consistently diminished, as were pulmonary capillary venous mean pressures. This explains some of the effects on cardiac dyspnea. There was no consistent change in brachial artery pressures. Respiratory volume, respiratory rate, pulse rate and oxygen consumption always increased.

ENSELBERG

Coe, R. P. K.: Instillation of Streptomycin into the Pericardial Sac in Tuberculous Pericarditis. Brit. M. J. 4696: 18 (Jan.), 1951.

The author reports a case of tuberculous peri-

carditis that did not respond to intramuscular streptomycin. However, weekly injections of 1 Gm. of streptomycin dissolved in 2 cc. of water, into the pericardial sac for six weeks brought rapid subsidence of fever and disappearance of the pericardial effusion.

BERNSTEIN

Latham, F.: The Oxygen Paradox. Experiments on the Effects of Oxygen in Human Anoxia. Lancet **260:** 77 (Jan.), 1951.

Sixty anoxia tests were carried out on 52 people at a simulated altitude of 20,000 ft. The subjects were divided into two groups, the first being anoxic for four minutes, and the second for five minutes. During the performance of a modified Lottig's writing test the incidence of errors during the recovery stages was calculated and compared. Further experiments were made on 8 of these subjects to determine the precise cardiovascular changes during the recovery stage from anoxia. For this purpose blood pressure, peripheral blood flow, and pulse rate were recorded with apparatus specially designed to give automatic and continuous records.

A paradox reaction to oxygen was demonstrated in 13 of the 52 subjects and seemed to begin between the ninth and twelfth seconds of the recovery stage from anoxia. Initially it is a disturbance of the central nervous system, as manifested by an increase in writing test errors which reaches its peak during the twelfth second of recovery. A slight secondary rise in the incidence of errors seems to coincide with the cardiovascular changes, which are most pronounced at about the thirtieth second of the recovery stage. These tests have also demonstrated the onset of muscular incoordination and mental confusion developing during this period. When the duration of the anoxia is increased, paradoxic symptoms in the form of faintness also increase, but the efficiency of the writing test deteriorates when the anoxia is severe.

It is considered probable that the neurologic manifestations of the paradoxic reaction follow a sudden impairment of cerebral circulation due to a rapid fall in systolic blood pressure when the breathing of oxygen is started again. A constitutional element is important in deciding whether the phenomenon is terminated by a cardiovascular collapse, about 15 seconds after the initial onset of nervous symptoms. The risk of a paradoxic reaction is entirely eliminated if oxygen is readministered slowly.

BERNSTEIN

Grob, D., and McGehee, A.: Observations on the Effects of the Automatic Blocking Agent, Bis-Trimethylammonium Pentane Dibromide (C_5) in Normal Subjects and in Patients with Peripheral Vascular Disease and Hypertension, and Comparison with Tetraethylammonium Chloride. Bull. Johns Hopkins Hosp. **87:** 616 (Dec.), 1950.

The effects of the intravenous administration of the autonomic ganglionic blocking agent, bis-trimethylammonium pentane diiodide or dibromide (C_5) were studied in 22 normal subjects, 16 patients with peripheral vascular disorders, and 25 patients with hypertension.

In 16 of the 22 normal subjects there followed a definite increase in the skin temperature of the extremities, somewhat more marked in the lower than in the upper extremities, and in the toes and fingers, than in the arms and legs. The peak of the response occurred within 20 minutes after the injection, and then the effect gradually tapered off over the next three or four hours. A similar type of change was noted in the patients with hypertension.

In 11 of the 16 patients with vascular diseases a definite increase in skin temperature was observed, while in the remaining 5, this did not occur. Seven of the patients were subsequently subjected to a sympathectomy. In the 4 of these who had had a good response with C_5, skin temperature readings obtained after sympathetic denervation were generally only slightly greater than the maximal increase noted after the use of the drug. In the other 3 patients, who had little or no increase in skin temperature after C_5, there was a much greater rise after lumbar sympathectomy.

The autonomic blocking action of C_5 was three to four times as prolonged as that of tetraethylammonium chloride, the former drug also being effective in much smaller doses. Furthermore, it produced none of the side effects that occurred after tetraethylammonium chloride.

ABRAMSON

Turner, J. P., and Schmidt, F. R.: Treatment of Scleroderma with Procaine. J.A.M.A. **144:** 1560 (Dec.), 1950.

Four patients with scleroderma were treated with multiple intravenous infusions of 0.1 and 0.2 per cent solutions of procaine hydrochloride over a period of several months. All 4 cases showed remarkable improvement in the color, texture and elasticity of the skin and mucous membranes, and increased mobility of the interphalangeal, metacarpal-phalangeal and temporal mandibular joints. There was no appreciable effect in one case on the course of ulcers noted over the bony prominences of the joints of the hands. The infusions were given slowly; an average of 30 minutes elapsing during each one. The dose per infusion ranged from 0.5 to 0.8 Gm. in 10 per cent dextrose and water.

KITCHELL

Oxley, J. M. R., and Cooke, A. M.: Temporal Arteritis—Two Cases Treated with Aureomycin. Lancet **260:** 89 (Jan.), 1951.

Two cases of temporal arteritis are described in which both patients were treated with Aureomycin. In case 1 the patient improved steadily while he was on Aureomycin, and the difference in his whole

appearance before and after starting the drug was remarkable. After two weeks he was afebrile and symptom-free. In case 2 the drug was badly tolerated, and its effect was less conclusive. However, the fall of temperature and return to normal of the temporal arteries soon after starting treatment with Aureomycin, and the relapse 48 hours after it had to be stopped, indicated a definite influence of the drug on the disease.

Although it is not claimed that the result of treatment in two cases is in any way conclusive, it is felt that the response to Aureomycin was sufficiently encouraging for this remedy to be tried by other workers.

BERNSTEIN

Fisher, C. W., Bennett, L. L., and Allahwala, A.: The Effect of Inhalational Anesthetic Agents on the Myocardium of the dog. Anesthesiology **12:** 19 (Jan.), 1951.

The effect of chloroform, ether, cyclopropane, divinyl ether, and nitrous oxide were studied in the dog heart-lung preparation. All these anesthetic agents produced cardiac dilatation of varying degree, presumably resulting from impairment of myocardial efficiency.

SAGALL

Sciarini, L. F., and Salter, W. T.: Chemical Correlatives of Digitalis Potency in Man, Cat and Pigeon. J. Pharmacol. & Exper. Therap. **101:** 167 (Feb.), 1951.

The authors obtained five fractions of tincture of digitalis by differential extraction, primarily with chloroform. The potency of each fraction was determined by the lethal effect after intravenous administration in the pigeon and cat, and by oral assay in man. The amount of digitoxin in each fraction was estimated by a fluorometric procedure. The results indicated that probably all of the oral activity for man is due to digitoxin which can be determined by microchemical measurements. This method offers a procedure for predicting the potency of digitalis preparations by microchemical analysis alone.

SAGALL

Rennick, B. R., Pardo, E. G., Gruhzit, C. C., and Moe, G. K.: The Role of the Thoracic Sympathetic Pathways in the Induction of Ventricular Ectopic Rhythms by Epinephrine and Cyclopropane. J. Pharmacol. & Exper. Therap. **101:** 176 (Feb.), 1951.

The threshold dose of epinephrine necessary to induce ventricular premature beats or tachycardia was determined in eight dogs under cyclopropane anesthesia. This threshold dose was increased slightly by tetraethylammonium chloride or by thoracic sympathectomy, but at the same time a reduction in the maximum pressor response was also observed. Restoration of the original arterial blood pressure by constriction of the aorta or blood infusion restored the original cardiac sensitivity to epinephrine. The authors concluded that the cardiac sympathetic innervation plays only a minor role in the induction of ventricular ectopic rhythms by epinephrine and cyclopropane.

SAGALL

PHYSIOLOGY

Jourdan, F., and Heyrand, J.: Influence of Accelerator Nerves of the Heart upon Experimental Nodal Rhythm. Compt. rend. Soc. de biol. **144:** 1378 (Oct.), 1950.

The authors studied the effect of stimulation of the stellate ganglion upon persistent nodal rhythm produced in rabbits by extirpation of the sinus node. Electrocardiographic tracings showed, following a short period of latency, a considerable acceleration of the ectopic rhythm and marked shortening of the P-R interval. The authors conclude that variations of both sympathetic and vagal tone may be responsible for variations of rate and P-R intervals observed in clinical cases exhibiting nodal rhythm.

PICK

Kaufmann, H., Delaunay, A., and Milanovitch, J. B.: The Effect of Weak High Frequency Currents upon the Contractions of a Fragment of the Heart of the Chicken Embryo in Tissue Culture. Arch. d. mal. du coeur **43:** 1083 (Dec.), 1950.

Short time application of a current of 24 volts and 426 kilocycles to a spontaneously beating fragment of the heart of the chicken embryo produced an increase of the force of contraction and a three to five time acceleration of their frequency. These alterations disappeared instantaneously with interruption of the stimulating current. If the action of the latter was prolonged over several minutes the contractions occurred in groups which were separated by periods of complete latency. The authors feel that this observation may represent an adequate method for the study of the phenomena of contractility and automatism.

PICK

Delaunay, A., Milanovitch, J. B., and Kaufmann, H.: Action Currents of Fragments of the Heart of the Chicken Embryo in Tissue Culture. Arch. d. mal. du coeur **43:** 1078 (Dec.), 1950.

Action potentials were obtained with the cathode tube electrocardiograph from a part of the heart of chicken embryos. The preparation continued to contract after being kept one to three hours in a tissue culture medium. The electrocardiogram consisted of a small and narrow RS complex of 0.04 second duration, followed by a tall, wide and diphasic (positive-negative) wave of about 1.5 second duration.

PICK

Milanovitch, J. B., Delaunay, A., and Kaufmann, H.: The Curve of Resistance of Fragments of the Heart of Chicken Embryo in Tissue Culture. Arch. d. mal. du coeur **43:** 1081 (Dec.), 1950.

In continuation of previous experiments the authors were able to record for the first time in form of a curve, variations of electrical resistance occurring in a fragment of the heart of the chicken embryo during its spontaneous contractions. The curve was diphasic, the positive part indicating diminution of resistance by 0.5 ohm and the negative phase its augmentation by 0.75 ohm. The initial, positive part of this oscillation occurred always more rapidly than its final (negative) portion.

PICK

Epstein, F. H., Goodyer, A. V. N., Lawrason, F. D., and Relman, A. S.: Studies of the Antidiuresis of Quiet Standing: The Importance of Changes in Plasma Volume and Glomerular Filtration Rate. J. Clin. Investigation **30:** 63 (Jan.), 1951.

The authors present data confirming earlier reports that a contraction of plasma volume, a decrease in renal clearances, and a diminished salt and water excretion occurs on quiet standing. However, this antidiuresis is not necessarily dependent upon a contraction of total plasma volume, since, even when plasma volume was expanded by rapid infusions of albumin, salt and water excretion diminished during standing.

The renal response to salt loads is conditioned in part by the rise in serum sodium concentration. In these studies the usual renal response to elevated serum levels (following hypertonic saline) could be prevented or reversed by standing upright. Apparently alterations in both composition and effective distribution of plasma are important in the regulation of glomerular filtration and tubular reabsorption of sodium.

WAIFE

RHEUMATIC FEVER

Hartman, S. A., and Bland, E. F.: Rheumatic Fever and Glomerulonephritis. Am. J. Med. **10:** 47 (Jan.), 1951.

The authors review the literature concerning the association of rheumatic fever and glomerulonephritis and present their own data. Acute glomerulonephritis and acute rheumatic fever occurred simultaneously in 2.5 per cent of 117 cases of clinically diagnosed acute nephritis. An additional 1.7 per cent had rheumatic heart disease. Thus, in the nephritis series 4.2 per cent had acute or chronic rheumatic involvement of the heart. In patients with rheumatic disease 5 per cent had acute or chronic glomerulonephritis at autopsy. Although the beta hemolytic streptococcus is the most frequent precipitating agent in both diseases, the determining factor as to organ susceptibility is unknown.

HARRIS

Smith, J. R., Saxton, J. A., Jr., and Fritz, H. C.: Syphilitic Cardiovascular Disease Combined with Chronic Endocardial Lesions Usually Attributed to Rheumatic Fever. Am. J. Med. **10:** 37 (Jan.), 1951.

Eight new cases of combined syphilitic aortitis and chronic endocardial lesions of probable rheumatic origin are presented along with a review of 17 cases found in the literature. Such combined lesions occur in 1 to 10 per cent of large autopsy series. The clinical possibility of such a combined etiology should be considered when overlapping evidence of either disease is discovered clinically. Coexistent syphilitic and rheumatic lesions may be present when aortic aneurysm, aortic insufficiency and a presystolic apical murmur are present or when mitral stenosis complicated by aortic regurgitation is found in the presence of clinical evidence of syphilis. The combination may also be present when aortic aneurysm and a diastolic murmur occur in a patient with a history of rheumatic infection.

HARRIS

Wilson, M. G., and Helper, H. N.: Effect of Pituitary Adrenocorticotropic Hormone (ACTH) in Acute Rheumatic Carditis. J.A.M.A. **145:** 133 (Jan.), 1951.

The authors report treatment of 11 consecutive patients ranging from 6 to 18 years of age, 6 of whom had initial attacks and 5, recurrent attacks. Adrenocorticotropic hormone (ACTH) was given intramuscularly in a daily amount of 30 to 100 mg. every six to eight hours for four to seven days. In all patients there was a disappearance of the associated signs and symptoms in 24 to 72 hours after the institution of therapy. In all these patients the level of circulating eosinophils before treatment ranged from 0 to 68. The authors feel that the circulating eosinophils are to be considered the most sensitive index to cortical hormone secretion. Three patients who had second courses of ACTH failed to show zero levels of eosinophils during treatment. The authors feel that a failure to drop to zero levels, or an eosinophil rise during treatment, is probably indicative of inadequate dosage; a fall in circulating eosinophils below normal range after discontinuation of therapy may indicate the necessity for readministration of ACTH. During therapy, circulating eosinophils should be maintained at zero levels. Four to 12 months after treating the 6 patients with initial attacks, 2 showed no evidence of residual cardiac damage, and 3 showed equivocal evidence. In 5 patients experiencing a recurrent attack there was no clinical evidence of increased cardiac damage.

From this work it would appear that the early treatment of acute carditis with adequate amounts of ACTH would shorten the course of the disease, result in minimal residual cardiac damage, and prevent death due to progressive carditis and congestive failure.

KITCHELL

ROENTGENOLOGY

Rembrandt, D., Scoville, W. B., and Whitcomb, B. B.: Complications of Angiography. J. Neurosurg. **8:** 110 (Jan.), 1951.

An experience with 147 carotid angiograms performed with 35 per cent Diodrast on 108 patients is reviewed as to complications that occurred. The patients were unselected.

Complications occurred in 14 cases, or nearly 10 per cent. Three of these were fatal. One fatality was attributed to postinjection cervical hematoma with resultant jugular vein obstruction. The other 2 were due to massive cerebral infarction.

Four cases developed permanent neurologic defects which were nonfatal, and were felt to be due to angiography. Only one of these was substantiated by pathologic examination. The remainder of the 14 cases had transient paralyses, convulsions, or other minor complications. In only one case did manifestations of drug sensitivity arise; and in this patient, no neurologic sequelae occurred.

The authors believe this high proportion of cerebrovascular accidents is due to vasospasm superimposed on an already impaired cerebral circulation. Prophylactic measures such as papaverine administration, sodium luminal, or stellate ganglion blocks are suggested.

FROBESE

Sposito, M., and Masini, V.: Hypertrophy of the Thymus Which Simulates in Adolescents an Increase of the Cardiovascular Image. Cardiologia **17:** 210, 1950.

This is a report of 12 children who were found to have a hypertrophied thymus which modified the x-ray appearance of the cardiovascular tree. The ages of the patients ranged from 10 to 19 years and there were 10 males. In all cases an anterior pneumomediastinum was performed which easily dissociated the thymus from the rest of the cardiovascular shadow.

WAIFE

SURGERY IN HEART AND VASCULAR SYSTEM

Swan, H., and Harper, F. B.: The Ligation of Major Arteries. Experimental Division of the Aorta. Surgery **28:** 958 (Dec.), 1950.

A method is described for ligation of such large vessels as the aorta. A long segment of artery is dissected free to permit the application of two nonerushing arterial clamps; between these the vessel is then severed. Both ends are sutured with silk, using a continuous stitch. This method appears to eliminate, as far as possible, the danger of hemorrhage from ligature failure or erosion.

ABRAMSON

Cahan, W. G., and Brunschwig, A.: Transection and Ligation of the Abdominal Aorta. Surgery **28:** 950 (Dec.), 1950.

A case is described in which the aorta was inadvertently entered in the process of taking a biopsy from a neighboring metastatic carcinoid, and consequently the vessel had to be ligated. Complete paralysis of the feet and legs followed, and the skin of the extremities turned a bluish-white color. However, the next day the feet became warm and pink. When the patient left the hospital, no signs of nutritional changes were noted on the extremities, but a large superficial ulceration was present over the sacrum. Complete loss of motor power still persisted. Six months after ligation of the aorta, the patient became oliguric and developed marked lymphedema of both lower extremities. He died 5 days later, and at autopsy diffuse carcinoma was present.

ABRAMSON

Shumacker, H. B., Jr., and Hampton, L. J.: Sudden Death Occurring Immediately after Operation in Patients with Cardiac Disease, with Particular Reference to the Role of Aspiration through the Endotracheal Tube and Extubation. J. Thoracic Surg. **21:** 48 (Jan.), 1951.

Five cases of sudden death occurring immediately after completion of a surgical procedure are reported. Four of the patients were children, one was an adult. In only one case was there any suggestion of an abnormal cardiac response during the course of the operation, although all demonstrated myocardial disease or congenital malformation of the heart. The fact that the disastrous changes occurred during suction upon a tube passed into the trachea through the endotracheal tube or during extubation was given significance as a possible mechanism for the cause of death.

ABRAMSON

Voris, H. C.: Complications of Ligation of the Internal Carotid Artery. J. Neurosurg. **8:** 119 (Jan.), 1951.

A series of 40 patients in whom the internal carotid artery was ligated for intracranial aneurysm is reviewed for complications. Seven deaths ensued, but only 6 were attributed to the procedure. The highest percentage of fatalities occurred in patients over 50 years of age. Various nonfatal neurologic complications occurred in an additional 9 cases.

Complications may occur within a few hours or later. The early manifestations are thought to be due to inadequate circulation. Late complications are caused by thrombosis or by emboli from a thrombus in the ligated internal carotid.

The Matas percutaneous carotid compression test is of value in predicting accidents only when it is positive. Bilateral carotid angiography and recordings of intracarotid pressure are advocated to test the adequacy of the collateral circulation prior to ligation.

Methods of preventing late complications caused by thrombosis include cervical sympathetic blocks

with procaine, administration of anticoagulants, and papaverine.

FROBESE

Taylor, F. W.: Saddle Embolus of the Aorta. Arch. Surg. **62:** 38 (Jan.), 1951.

After reviewing the findings associated with sudden occlusion of the distal end of the aorta by an embolus, the author reported a case of his own which was successfully treated by embolectomy 6 hours after onset of the condition. An incision was made in the right common iliac artery and the embolus from the aorta was expressed through this opening. Both iliac arteries filled immeidately and pulsated normally, and a pulse was felt in the right dorsal pedal artery. None was observed in the left dorsal pedal artery, although the foot became warm. This pulse returned the next day. The postoperative recovery was uneventful. The patient regained complete function in his lower extremities. He lived for 14 months after embolectomy. His death was caused by a myocardial infarction.

ABRAMSON

Ochsner, A., De Bakey, M. E., and De Camp, P. T.: Venous Thrombosis. Surgery **29:** 24 (Jan.), 1951.

The authors analyzed 580 cases of thrombophlebitis and phlebothrombosis observed in a large general hospital over a period of seven years. They found that despite the various prophylactic measures that are being carried out on a large scale, the incidence of thromboembolism was increasing. The age incidence of fatal pulmonary embolism followed closely the age distribution of thrombosis. In approximately one-half of the former cases there was no clinical evidence of the presence of conditions which might lead to the production of emboli.

About one-fourth of the cases of thromboembolism occurred postoperatively, while the next largest number was observed in patients with heart disease. The highest mortality rate was noted in the latter group, while the lowest was present on the surgical and obstetrical services.

ABRAMSON

Hufnagel, C. A., Roe, B. B., and Barger, A. C.: A Technique for Producing Pulmonary Artery Stenosis. Surgery **29:** 77 (Jan.), 1951.

A technic for producing pulmonary artery stenosis in dogs is described. The thorax is opened on the left side, and the heart and the pulmonary artery are exposed, the latter being isolated along its full length from valve ring to bifurcation. A curved clamp is applied to the superior aspect of the vessel and slowly closed to produce a fusiform narrowing of the lumen. A continuous mattress suture is placed along the inside of the clamp, the latter is removed, and the occluded segment is incised along the suture line.

This method of partial occlusion is technically safe and can be applied to the aorta and other great vessels. The complication of vessel wall erosion has been avoided by the absence of external constriction.

ABRAMSON

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ANNUAL MEETING

The Annual Meeting and Twenty-Fifth Scientific Sessions of the American Heart Association will be held at the Hotel Statler, Cleveland, Ohio, April 18–20, 1952. All of those planning to attend should make room reservations directly with the Hotel Statler in Cleveland at the earliest possible date.

The Chairman of the Program Committee for the Annual Scientific Sessions is Dr. Irvine H. Page, Cleveland Clinic, 2020 East 93 Street, Cleveland 6, Ohio. All who desire to present papers at the meeting in Cleveland should forward to Dr. Page an abstract (in triplicate) of the proposed presentation of not more than 300 words. As a departure from previous practice, arrangements will be made at this meeting for a special session to present papers dealing with the basic science aspects of cardiovascular disease.

The deadline for the receipt of abstracts is January 1, 1952.